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REVIEW

# Drug Delivery System Targeting Cancer-Associated Fibroblast for Improving Immunotherapy

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**Abstract:** Cancer-associated fibroblasts (CAFs) are a heterogeneous population of non-malignant cells that play a crucial role in the tumor microenvironment, increasingly recognized as key contributors to cancer progression, metastasis, and treatment resistance. So, targeting CAFs has always been considered an important part of cancer immunotherapy. However, targeting CAFs to improve the efficacy of tumor therapy is currently a major challenge. Nanomaterials show their unique advantages in the whole process. At present, nanomaterials have achieved significant accomplishments in medical applications, particularly in the field of cancer-targeted therapy, showing enormous potential. It has been confirmed that nanomaterials can not only directly target CAFs, but also interact with the tumor microenvironment (TME) and immune cells to affect tumorigenesis. As for the cancer treatment, nanomaterials could enhance the therapeutic effect in many ways. Therefore, in this review, we first summarized the current understanding of the complex interactions between CAFs and TME, immune cells, and tumor cells. Next, we discussed common nanomaterials in modern medicine and their respective impacts on the TME, CAFs, and interactions with tumors. Finally, we focus on the application of nano drug delivery system targeting CAFs in cancer therapy.

**Keywords:** cancer-associated fibroblasts, drug delivery, nanomedicine, tumor microenvironment, cancer immunotherapy

## Introduction

Nowadays, cancer remains one of the leading causes of death globally, accounting for more than 10 million deaths each year. CAFs has garnered increasing attention as therapeutic targets due to their indispensable role in tumor progression and their unique ability to remodel the tumor.[1] Unlike other stromal or immune cells, CAFs are abundant and dynamically interact with both cancer cells and the surrounding TME, playing a pivotal role in tumor survival, proliferation, and metastasis.[2,3] CAFs influence tumor biology through several distinct mechanisms, including remodeling the extracellular matrix (ECM), promoting angiogenesis, secreting growth factors and cytokines, and inducing immune evasion.[4,5] These multifaceted functions make CAFs indispensable for sustaining tumor dynamics and an ideal target for therapeutic intervention compared to other cell types within the TME. More and more research have confirmed the relationship between CAFs and different cancers, finding that CAFs play a key role in all aspects of tumor,[6] such as promoting tumor growth and spread, improving drug resistance, remodeling TME and immunosuppression. One prominent mechanism involves the transfer of exosomes directly to cancer cells. For example, CAFs exert their roles by directly transferring exosomes to colorectal cancer (CRC) cells, leading to a significant increase of miR-92a-3p levels in CRC cells, which causes metastasis and chemotherapy resistance in CRC patients.[7] Additionally, there are different subtypes and phenotypes of CAFs in different tumors, which increases the difficulty of unified targeting of CAFs to treat cancer. However, it also adds the opportunities for specific targeted therapies about different cancers at the same time.[8]

With the development of targeted drug therapy, the advantages of nanomaterials have been continuously explored. Different nanomaterials possess unique physicochemical properties that offer significant advantages for improving drug delivery and treatment outcomes, medical nanomaterials can be broadly categorized into organic and inorganic types.[9–11]

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These materials can be precisely engineered to target CAFs, thereby modifying the TME to bolster antitumor immunity. Targeting CAFs with nanomaterials disrupts the fibrotic stroma, reduces extracellular matrix (ECM) deposition, and mitigates the immunosuppressive milieu.[12] Moreover, this disruption facilitates enhanced penetration of immune cells and therapeutic agents into the tumor core.[13] Furthermore, nanomaterials can be designed to carry and release immunomodulators, thereby boosting the activation and proliferation of immune cells within the TME.[13] Nanoparticles can be designed to target specific components of the immune system or TME, thereby enhancing the specificity and efficacy of immunotherapeutic agents.[14] For instance, nanoparticles targeting CAFs can help dismantle the immunosuppressive stroma, thereby improving the infiltration and activity of cytotoxic T lymphocytes.[15] In a word, nanomedicine represents the forefront of cancer therapy and offers targeted delivery systems that could reduce systemic toxicity and improve therapeutic indices.[16]

In conclusion, nanomedicine targeting CAFs integrates significant potential for advancing cancer immunotherapy. These systems utilize the unique properties of nanomaterials to precisely regulate the TME, enhancing both local and systemic immune responses. This enhancement improves anti-tumor immune responses and treatment outcomes, potentially improving survival rates and the quality of life for cancer patients.

# Biological Characteristics of CAFs

## Heterogeneity and Diversity in the Origin of CAFs

CAFs originate from diverse sources, with cells being the most common. For instance, normal fibroblasts may be recruited by tumor cells to tumor tissue and then converted into CAFs.[17] Furthermore, CAFs result not only from the transformation of endothelial, epithelial, mesenchymal stem cells, adipocytes and other cells, but also from the differentiation of tumor stem cells.[18–20] Additionally, some studies indicate that the sources of CAFs can also be influenced by physiological status, tumor type, environmental factors, and other variables.[21] For example, in breast cancer, we find that adipocytes can be dedifferentiated into CAFs.[22] Notably, some studies have proven that the lack of certain substances in a specific environment can also cause the differentiation of CAFs.[23] For example, in Jerome Thiery's article, he pointed out that vitamin A or D deficiency can also promote CAF differentiation in some cases.[24] However, further evidence and research are required to investigate the origins of CAFs across various environments. Moreover, different subtypes of CAFs exhibit distinct biological characteristics and functions,[25,26] such as invasive CAFs, immunosuppressive CAFs, stromal CAFs, and degenerative CAFs. Invasive CAFs are mainly involved in tumor invasion and metastasis, immunosuppressive CAFs help tumor cells evade immune surveillance, stromal CAFs are primarily responsible for constructing the tumor microenvironment, while degenerative CAFs are mainly involved in the formation of tumor drug resistance. Furthermore, CAFs in the studied tumor types, we can roughly divide CAFs into three categories (Figure 1), namely myofibroblasts (myCAFs), inflammatory CAFs (iCAFs), and antigen-presenting CAFs (apCAFs).[27–29] Interestingly, some studies suggest that balancing the proportions of CAF subgroups could be a significant clinical strategy,[29] therefore, we could potentially provide specific treatments for patients based on different CAFs and their number in the future.[30] In summary, distinct CAF subtypes are distributed across various tissues and organs.[31] There are multiple subtypes of tumor-associated fibroblasts, each of which may play roles in different diseases and tissues.[32] Understanding the characteristics and functions of these CAF subtypes is crucial for providing new ideas and directions for targeted therapy in the future,[33] as it will help us deeply understand the tumor microenvironment and its regulatory mechanisms.

## Diversity of CAFs Markers

CAFs and their markers both play an important role in the development of tumors, especially, there are different biological functions of their markers in the TME. Therefore, understanding the functions and roles of these markers may be a vital part of comprehending cancer immunotherapy better. Up to now, it is widely acknowledged that the markers of CAFs have significant clinical application value.[34] For example, these markers are invaluable for identifying and monitoring the presence and development of tumors. For simplicity, clinicians can diagnose tumors and evaluate their severity by detecting these markers in blood or tissue samples. Moreover, these markers can predict tumor responses to therapies and monitor treatment outcomes.[35] So, we think these markers must have surprising clinical application prospects in the future.[36]

The discovery of markers is a long and hard process. In the 1970s, Gabbiani et al first identified α-smooth muscle actin (α-SMA) while studying granulation tissue during wound healing. Meanwhile, so far, α-SMA is still one of the

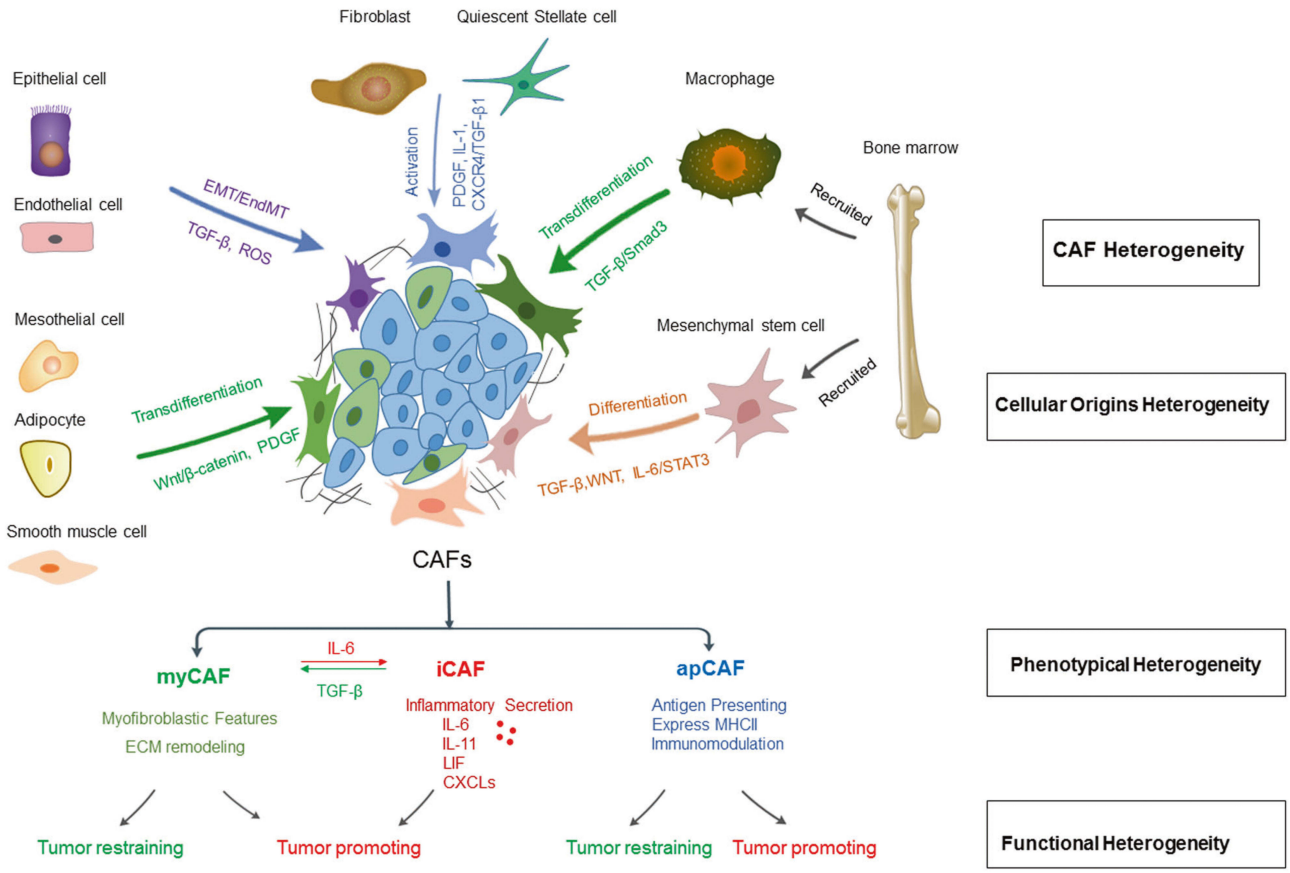


**Figure 1** The Origin of CAFs. Fibroblast heterogeneity arises from diverse precursor cell origins, phenotypic variation, and distinct functions of each subset. Key cellular sources include local stellate cells, fibroblasts, and bone marrow-derived MSCs and macrophages. The main CAF subsets—myCAFs, iCAFs, and apCAFs—exhibit unique biological features, contributing to cancer progression's phenotypic and functional diversity. These CAF subsets are dynamic and can interconvert through specific signaling pathways, such as TGFβ or IL-6, facilitating transitions between iCAFs and myCAFs. Reproduced from Yang D, Liu J, Qian H, Zhuang Q. Cancer-associated fibroblasts: from basic science to anticancer therapy. Exp Mol Med. 2023;55(7):1322–1332. http://creativecommons.org/licenses/by/4.0/.[31].

classic markers of CAFs and is usually used to identify CAFs.[37,38] However, recent studies have shown that CAFs of α-sma+ may have both pro- and anti-tumor properties.[39,40] Furthermore, fibroblast activation protein (FAP) as a membrane protein is another classic marker,[41] which was discovered by scientists in interstitial cells and certain types of cancer in the early 1990s. Platelet-derived growth factor receptor (PDGFR), which is highly expressed in CAFs and involved in the activation of CAFs and tumor promotion, was found in platelets and subsequent molecular cloning experiments, by Jan-Åke Gustafsson and Charles-Henri Heldin in 1978.[42] With advancements and innovations in scientific detection methods, scientists have identified numerous different CAF markers through techniques like single-cell sequencing.[43] Additional markers of CAFs include Vimentin, fibronectin (FN), laminin (LN), matrix metalloproteinases (MMPs), epithelial cell adhesion molecule (EPCAM), synovial glycoprotein (SGR), and mannose-binding lectin (MBL).[44–47] Furthermore, more interestingly, in breast cancer-associated fibroblasts, we find that specific genes such as NOTCH3 and HES4 act as markers involved in CAF self-renewal and proliferation.[48] This discovery may offer a novel approach to integrating gene technology with these markers. In general, although we have discovered many new markers, the biomarkers of fibroblasts we identified are still limited so far. For a more in-depth discussion, how do we distinguish between fibroblasts, CAFs, or different subtypes of CAFs by using simple markers is crucial, but it still remains a challenge.[45] Hopefully, this challenge will be resolved in the near future.

## Interactions Between CAFs and Tumor Cells

Studies have indicated that the quantity and activity levels of CAFs are closely associated with tumor prognosis in cancer patients. The impact of CAFs on tumor development and prognosis is multifaceted and influenced by various factors.[49]

However, during the development of cancer, CAFs interact with tumor cells by expressing extracellular signaling molecules such as osteopontin (OPN) and hepatocyte growth factor (HGF), thereby influencing tumor cell proliferation, invasion, and migration.[50] Subsequently, in the TME, CAFs regulate tumor development by modulating metabolic activities, including glucose and pH balance adjustments,[51] and by influencing mitochondrial function, thereby participating in tumor cell energy metabolism. Other research has shown that mechanical forces generated by CAFs can affect tumor cell movement and morphology by activating intracellular cytoskeletal systems and signaling pathways,[52] which may speed the spread of tumors. Exosomes, small extracellular vesicles, mediate intercellular signaling and maintain tissue and organ stability through various mechanisms. Exosomes secreted by CAFs also play a crucial role in influencing tumors. For example, in the study by Piwocka et al, CAF-derived exosomes carrying microRNA-296-3p were found to promote malignant behaviors such as proliferation, migration, invasion, and drug resistance in ovarian cancer cells, this also suggests microRNA-296-3p as a potential diagnostic marker and therapeutic target.[53] Then Zhang et al discovered that miR-522 enhances tumor cell resistance to chemotherapeutic drugs and inhibits ferroptosis in gastric cancer cells by targeting ALOX15 to suppress lipid peroxidation. Their research unveiled a novel intercellular pathway involving USP7, hnRNPA1, exo-miR-522, and ALOX15, which regulates lipid peroxidation levels in tumor cells, impacting their chemotherapy sensitivity.[54]

On the other hand, tumors or tumor cells can also influence CAFs. Activation pathways of CAFs include direct interaction with tumor cells and activation through the Notch signaling pathway. Additionally, matrix remodeling by CAFs amplifies their activation, creating a positive feedback loop.[55] Interestingly, in some cases, tumor cells can induce the "reverse Warburg effect" in CAFs, enriching energy in CAFs and promoting glycolytic pathway activation.[31] However, in pancreatic ductal adenocarcinoma (PDAC), cancer cells induce autophagy in CAFs, leading to the secretion of non-essential amino acids like alanine, which support cancer cell needs by promoting the tricarboxylic acid cycle and lipid biosynthesis.[56]

In conclusion, CAFs are inextricably linked with tumors and tumor cells, making CAFs are not only therapeutic targets but also integral components of cancer treatment strategies.[55] Therefore, we think future treatment strategies should consider tailored approaches based on different tumor types and CAF subtypes, this is the only way to address the challenge of one-size-fits-all treatments being insufficient and provide personalized treatment.[57]

## The Interaction Between CAFs and TME

The tumor microenvironment (TME) is a complex ecosystem comprising various cell types, extracellular matrix (ECM), blood vessels, and immune cells. While CAFs are crucial components of the tumor microenvironment, interacting with tumor cells and playing significant roles in tumorigenesis and development (Figure 2).[58] Current research reveals that CAFs can influence tumor immune evasion by activating or inhibiting the immune system. They also promote angiogenesis, regulate inflammatory responses, remodel the ECM, and induce CAF differentiation, among other functions.[59,60] These activities occur within the tumor microenvironment, emphasizing the importance of investigating CAF interactions within the TME. Additionally, CAFs and the TME interact reciprocally, for example, with CAFs regulating the TME by secreting growth factors, chemokines, and other molecules that promote tumor formation.[61] These regulatory activities include remodeling extracellular matrix and metabolic reprogramming.[62] Moreover, CAFs engage in transmembrane signaling with other TME cells through various pathways, influencing disease progression.[63] For example, CAFs secrete chemokines such as PDGF, IL-6, and TNF-α, which attract and recruit other cells in the TME to the tumor site, thereby further promoting tumor growth and metastasis.[64] Recently, some studies highlighted the critical roles of exosomes in the TME for cancer and inflammation.[65] Exosomes facilitate communication between CAFs and tumor cells, contributing to tumor occurrence, development, and metastasis.[66,67] For instance, research by Sun et al has demonstrated that exosomal ncRNAs from CAFs participate in CRC microenvironment formation and may be linked to resistance mechanisms in CRC patients undergoing radiotherapy.[68] Furthermore, the biological characteristics and functions of CAFs are also influenced by the tumor microenvironment. For instance, in environments with elevated levels of hyaluronic acid (HA) or oxidative stress, CAFs may be stimulated to exhibit more active tumor promoting behavior.[69] Despite significant progress, many uncertainties persist regarding CAF functions in different TMEs,[70,71] and further breakthroughs are expected.

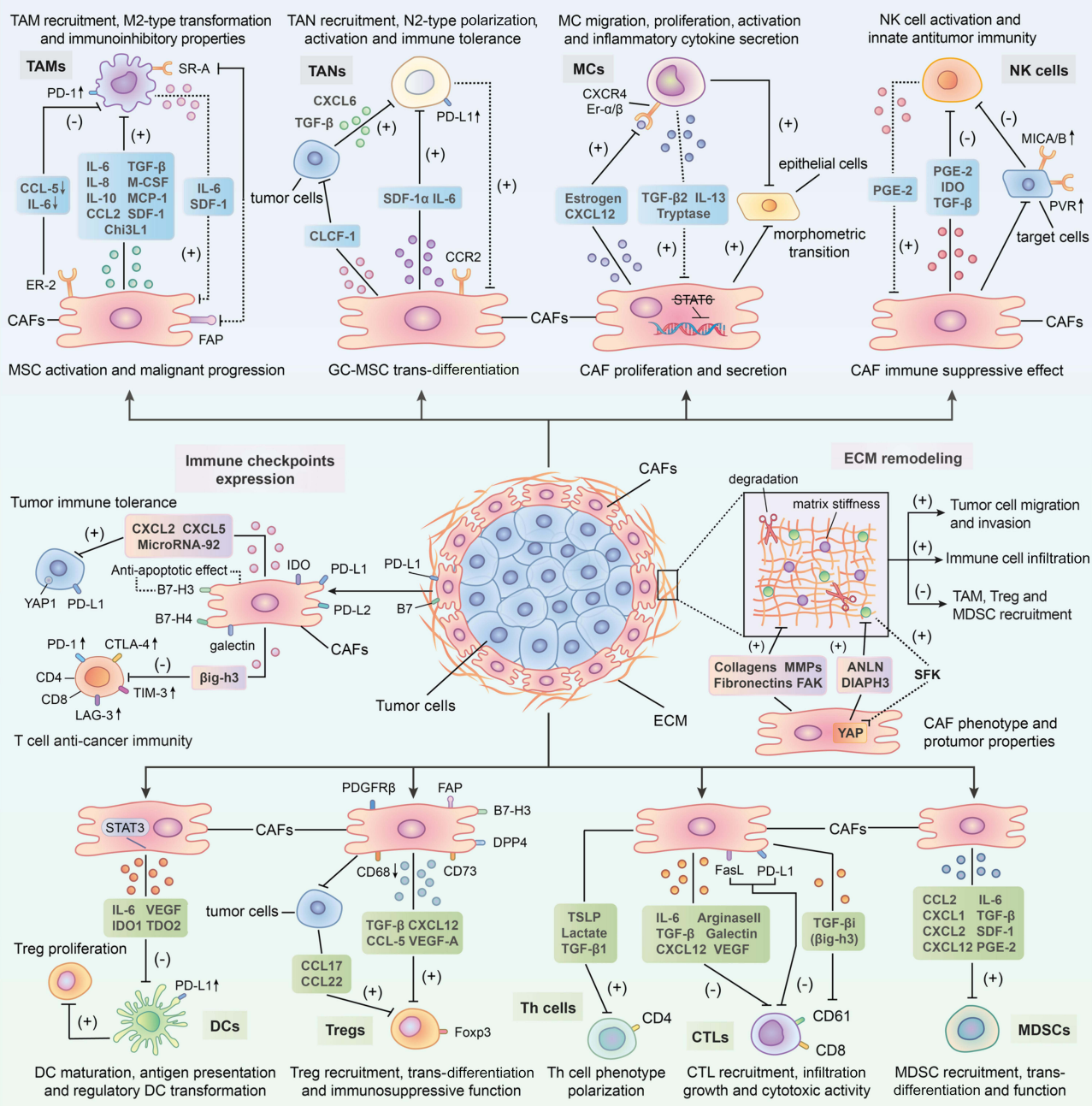


**Figure 2** The Interaction between CAFs and TME. This figure highlights the role of CAFs in shaping the TME. CAFs interact with immune cells (eg, TAMs, TANs, NK cells) and remodel ECM, promoting tumor invasion, immune suppression, and immune checkpoint expression (eg, PD-L1, B7-H3). By recruiting immunosuppressive cells like Tregs and MDSCs and suppressing CTL activity, CAFs establish a pro-tumorigenic TME, underscoring their potential as therapeutic targets. Reproduced from Mao X, Xu J, Wang W, et al. Crosstalk between cancer-associated fibroblasts and immune cells in the tumor microenvironment: new findings and future perspectives. Mol Cancer. 2021;20 (1):131. http://creativecommons.org/licenses/by/4.0/.[46].

## The Interaction Between CAFs and Immune Cells

Immune cells are an important part of the TME, and they play complex dual roles. In most cases, CAFs play a positive role in tumor immune suppression, closely intertwined with immune responses and immune cells. Therefore, we delve into the interactions between CAFs and specific immune cells. Generally, CAFs can interact with T cells, helper T cells, natural killer cells, macrophages, and myeloid-derived suppressor cells (MDSCs).[24,52,72,73] For instance, a recent study by Ying et al highlighted that CAFs can inhibit T cell activation through inhibitory receptors like programmed death ligand 1 (PD-L1), thereby evading immune surveillance and attack.[74] Concurrently, Zeng et al found in vitro that macrophages expressing M2 phenotype-related genes can enhance resistance to chemotherapy in


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CAFs and breast cancer cells.[75] Furthermore, CAFs can even regulate cancer cell proliferation and migration by secreting extracellular signaling molecules such as growth factors and chemokines, recruiting immune cells to participate in cancer development.[76] However, some studies indicated that different CAF subtypes have been observed to modulate the distribution and activity of immune cells within the tumor microenvironment in varying ways.[58] Additionally, in a recent study through spatial transcriptomics analysis, Chen et al discovered distinct distributions and interactions of different cell types within the lung cancer tumor microenvironment. For example, CAFs and malignant cells typically cluster together to form the tumor core, whereas immune cells are predominantly located at the tumor periphery. Furthermore, various immune cell types such as macrophages and dendritic cells exhibit unique distribution patterns and functional characteristics.[77]

## CAFs as Potential Therapeutic Targets

CAFs are a key component of the TME and are widely involved in and drive tumor progression. Multiple studies have shown that CAFs can secrete various growth factors, cytokines, chemokines, and matrix remodeling molecules to significantly alter the characteristics of the tumor microenvironment,[78–80] which promotes tumor cell proliferation, angiogenesis, and immune escape. Therefore, these complex biological interactions between CAFs and TME make CAFs an important target for cancer immunotherapy.[81]

CAFs can produce and secrete large amounts of ECM proteins, such as collagen and fibronectin,[80,82] which not only provide structural support for tumors but also promote tumor cell migration and invasion.[80] For instance, CAFs are known to activate the transforming growth factor-beta (TGF-β) pathway, which results in increased ECM deposition and fibrosis. This fibrosis creates a physical barrier that prevents immune cells from infiltrating the tumor and limits the delivery of therapeutic agents.[80,83] By targeting CAFs or disrupting the TGF-β signaling pathway, it is possible to degrade the ECM and improve the penetration of immune cells and drugs into the tumor core.[84,85] Moreover, CAFs contribute to the creation of an immunosuppressive TME by secreting cytokines such as IL-6 and CXCL12,[82,83] which can inhibit cytotoxic T lymphocyte (CTL) activity in different ways, ultimately allowing tumor cells to evade immune surveillance.[86] Up to now, the CXCL12/CXCR4 signaling axis between CAFs and immune cells has been widely identified as a key mediator of immune evasion.[87,88] In this regard, by using this signaling axis of CXCR4 antagonists, Biasci et al have confirmed the infiltration and enhancement of CTL activity within the tumor, which enhances the anti-tumor immune response.[89] Additionally, in the new research of Sunil Singh et al, they found that CAFs can activate c-Met receptors on tumor cells by secreting hepatocyte growth factor (HGF) in triple negative breast cancer, and then promote proliferation and resistance to tyrosine kinase inhibitors.[90] Additionally, several related studies have also suggested that targeting the HGF/c-Met axis presents another potential strategy to overcome drug resistance mediated by CAFs.[91,92] Another promising strategy is to reprogram CAFs instead of completely eliminating them.[93,94] However, CAFs exhibit significant heterogeneity, with different subtypes displaying both pro tumorigenic and potential anti-tumor properties.[94] So it may be an extremely challenging task to reprogram different types of CAFs and explore their potential therapeutic effects. But in recent studies, the use of nanoparticles to specifically target CAFs has demonstrated considerable promise in enhancing treatment efficacy.[95,96] By combining new advances in nanomaterials, we can utilize precise drug delivery or specific pathways associated with CAFs to targets CAFs, which holds great significance for advancing cancer immunotherapy.

# Nanomaterials and Tumor Targeted Therapy

## Classification of Nanomaterials

In recent years, the rapid development of nanomaterials and their increasing application in medicine have made medical nanomaterials a perennial research hotspot (Figure 3). In this review, we explore some nanomaterials discovered by modern medicine, such as nanoparticles, biomimetic nanoparticles, inorganic nanomaterials, organic-inorganic hybrid nanomaterials, conventional nanomaterials, and their specific roles in biological systems (as summarized in the Table 1).

So far, we have known that tumor cells are influenced by various factors, including TME and CAFs, while nanomaterials can play direct or indirect roles in disrupting tumor cell infiltration, invasion, and proliferation. For instance, a recent experiment demonstrated that gold-silver core-shell hybrid nanomaterials can significantly inhibit the

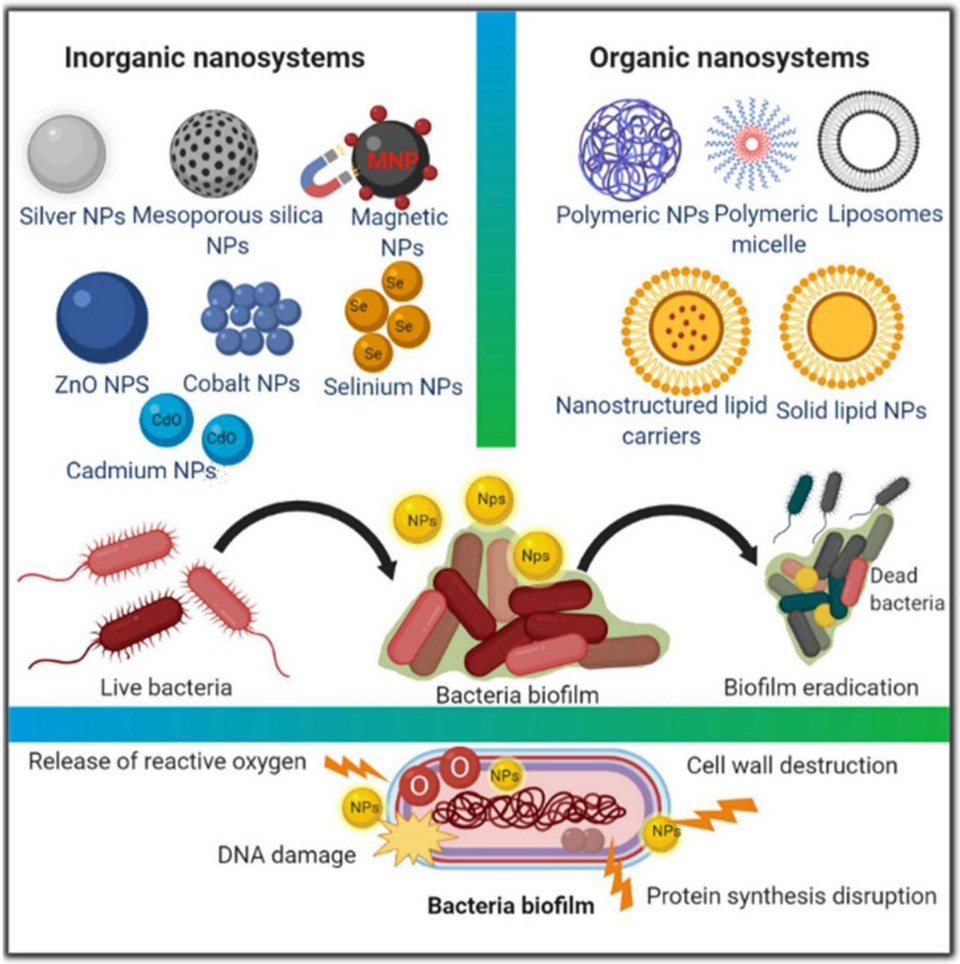


**Figure 3** Classification and Mechanisms of Nanosystems. Nanosystems can be classified into inorganic and organic types, based on their matrix characteristics and the materials they are composed of. Inorganic nanosystems include silver nanoparticles (NPs), mesoporous silica NPs, magnetic NPs, ZnO NPs, cobalt NPs, selenium NPs, and cadmium NPs, which are designed for high stability and reactive properties. Organic nanosystems, such as polymeric NPs, polymeric micelles, liposomes, nanostructured lipid carriers, and solid lipid NPs, provide biocompatibility and versatility for drug delivery. Reproduced from Eleraky NE, Allam A, Hassan SB, Omar MM. Nanomedicine fight against antibacterial resistance: an overview of the recent pharmaceutical innovations. Pharmaceutics. 2020;12(2):142. http://creativecommons.org/licenses/by/4.0/).[97]

migration of adenocarcinoma cells promoted by fibroblasts and reduce their proliferation, thereby curtailing metastatic spread.[111] In another study, ZnO@CuS nanoparticles enhanced tumor cell sensitivity to photothermal therapy and suppressed cell migration by generating free radicals.[112] Furthermore, combining monoclonal antibodies with nanomaterials enables precise targeted therapy, sparing normal tissues.[113] Additionally, the strategy of combining multiple drugs

**Table 1** Classification of Nanomaterials

| Classification | Material Name | Role | Reference |
|---|---|---|---|
| Nanoparticles | Gold nanoparticles (AuNPs) | Modulate CAF secretion to slow the progression of pancreatic tumors in situ | [98,99] |
| | Photosensitizers (such as zinc phthalocyanine, heme) | Release reactive oxygen species (ROS) under light exposure to induce cancer cell death. | [35] |
| Biomimetic nanoparticles | Nanoparticles modified by protein or peptide | Suppress the metastasis of breast cancer through targeted interventions | [100] |
| | Nanoparticles based on artificial collagen matrix | | |
| | Artificial micro robot inspired by bacteria | | |

(*Continued*)


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**Table 1** (Continued).

| Classification | Material Name | Role | Reference |
|---|---|---|---|
| Inorganic nanomaterials | Polyvinyl alcohol nanoparticles | Improve the therapeutic efficacy of antitumor drugs by employing complementary strategies | [100–103] |
| | Long chain polyethylene glycol nanoparticles | | |
| | Polymeric nanomicelles | | |
| | Polylactic acid, long-chain polyethylene glycol, polyvinyl alcohol, folate modified nanoparticles, liposome nanoparticles, pH sensitive nanoparticles, heat sensitive nanoparticles, liposome nanoparticles with mitomycin on the surface | | |
| | Ferritin | It can serve as an effective drug delivery system, demonstrating great potential in cancer treatment | [35] |
| | Graphene oxide | It kills cancer cells through multiple mechanisms, offering versatile therapeutic approaches | [99,104,105] |
| Organic inorganic hybrid nanomaterials | Magnetic nanoparticles | It can be utilized as a drug delivery system, showing significant potential in cancer treatment | [100,101] |
| | Polymer nanomaterials | It eliminates cancer cells through various mechanisms, offering diverse therapeutic options | [99,104,105] |
| | Liposome nanoparticles | Its positioning and controllability enable precise treatment and diagnosis of tumors | [106] |
| | Fatty acidified peptide nanoparticles | Improves the therapeutic efficacy of antitumor drugs by optimizing their delivery | [93,102,103] |
| | Nanovesicle | Increases drug accumulation in tumor tissues while minimizing toxicity and side effects | |
| | Nanowires | Penetrates the blood-brain barrier, enabling effective treatment of brain tumors | |
| | Nanotube | Directly interacts with tumor cells to induce apoptosis or inhibit their growth | |
| | Fibronectin (FN), transferrin receptor, integrin, MMP-2, TFR, | Modulates cytokine and chemokine levels within the tumor microenvironment, thereby influencing tumor cell migration and localization. | [107] |
| | Liposomes | Engages directly with tumor cells to induce apoptosis or inhibit their proliferation | [108] |
| | Drug loaded nanospheres, drug loaded nanotubes, drug loaded Nanovesicles | Targets specific receptors on the surface of tumor cells, enabling selective killing of cancer cells | [109,110] |
| Conventional nanomaterials | Polylactic acid, long-chain polyethylene glycol, polyvinyl alcohol, folate modified nanoparticles, liposome nanoparticles, pH sensitive nanoparticles, heat sensitive nanoparticles, liposome nanoparticles with mitomycin on the surface | Increases drug accumulation in tumor tissues while minimizing toxicity and side effects; PH sensitive nanoparticles can release drugs in acidic environment; Thermosensitive nanoparticles can kill tumor cells by heating; Utilizes lipids conjugated with mitomycin on the surface for efficient drug delivery and enhanced therapeutic outcomes | [100–103] |

with nanomaterials offers novel approaches to cancer treatment.[113] At present, radiotherapy and chemotherapy remain the pivotal methods in cancer treatment, with nanomaterials substantially enhancing their efficacy.[114] For example, that gold nanocages coupled with radioactive isotopes enhance radiotherapy effectiveness by forming radiolabeled markers.[107] Furthermore, another study that nanoscale radiosensitizers improve tumor cell sensitivity to radiation, thereby boosting radiotherapy outcomes.[115] Moreover, nanomedicines, which carry chemotherapeutic drugs, can specifically target specific tumor cell receptors to increase drug accumulation and enhance chemotherapy efficacy.[116] Addressing tumor drug resistance is critical, and nanomaterials offer promising solutions. Certain nanoliposomes prolong drug circulation to increase bioavailability,[100] while nanomicelles can bind to multidrug resistance-associated proteins, facilitating drug entry into tumor cells.[117,118] In the experiment of Cheng et al, they elaborated that a kind of gold nanocage pH-sensitive conjugates releases anticancer drugs in response to acidic conditions, enhancing drug concentration in tumor tissues and radiotherapy efficacy.[119] Notably, nanoparticles have been shown to traverse the blood-brain barrier in multiple studies, modifying the TME and enhancing drug efficacy.[101,102] Therefore, nanomedicines may have great application potential in neurological diseases. Lastly, beyond therapeutic applications, some nanomaterials offer diagnostic functionalities, such as fluorescence and magnetic resonance imaging capabilities. For example, iron oxide nanomaterials enable the observation of tumor location and size through advanced magnetic resonance imaging techniques.[44]

In conclusion, nanomaterials will be increasingly important roles widely used in the field of Medicine. However, while exploring new materials, we should further provide their applications in the medical field.[97] Especially in the immunotherapy of cancer, there are still many difficulties that need more time to solve.

## Nanomaterials as Multifunctional Tools for Targeting and Modulating CAFs

From numerous previous studies, it has been demonstrated that nanomaterials have significant effects on CAFs.[35] On one hand, some nanomaterials served as carriers for chemotherapeutic drugs or bioactive molecules, delivering them directly to CAFs, and thereby enhancing therapeutic efficacy while minimizing impact on healthy tissues. For instance, Li et al developed reversibly bonded nanoparticles capable of delivering anticancer drugs precisely to CAFs, illustrating their potential in targeted therapy.[120] Additionally, in a review by Aljabali AA et al, they highlighted the impact of nanomaterials on the immune system, some nanomaterials have immunomodulatory properties, facilitating the clearance or control of CAFs by modulating immune responses.[121] On the other hand, specific nanomaterials are often designed to target molecules on the surface of CAFs, such as FAP, to inhibit their activity.[122] For example, Zhou et al developed α FAP-Z@FRT nanomaterials, which selectively target FAP expression in CAFs without affecting non-tumor tissues. Moreover, different nanomaterials can also affect CAFs in many aspects. For instance, Li et al utilized a complex nanocomposite, which involves graphene oxide, gold nanoparticles, and fluorescent dyes, then it is observed that this composite material can release chemicals to selectively eliminate CAFs upon near-infrared laser irradiation.[120] Additionally, certain nanomaterials act as carriers for photothermal therapy, generating heat upon exposure to light to induce CAF apoptosis.[35] For instance, Mukherjee et al demonstrated that 20 nm gold nanoparticles transform CAFs into a quiescent state rich in lipids, to inhibit matrix deposition. Similarly, many studies point out gold nanocages, nanoparticles, and nanorods can all target and suppress CAF growth and function through photothermal effects.[98,123] To be more specific, gold nanocages disrupt CAF structures via photothermal therapy, thereby impeding their proliferation and secretory functions.[123] And gold nanoparticles specifically target CAFs to inhibit their proliferation and migration capabilities.[98] More interestingly, so far, recent studies have reported paradoxical effects of certain nanomaterials on CAFs, stimulating their proliferation and migration.[93,119] So, these interesting studies may provide a new reverse thinking for targeted therapies of CAFs and cancer immunotherapy. Moreover, we discovered certain nanomaterials enable the detection of gene expression and products in CAFs, which may facilitate studies on their role in tumor development in the future.[116] Although these new ideals currently lack practical applications, these advancements hold significant promise for future research and clinical implementation.

## Nanomaterials and Their Interactions with CAFs in the TME

Research on how nanomaterials interact with CAFs within the TME is a key area in modern cancer therapy.[124] Nanomaterials modulate cellular-level biological activities within the TME, due to their unique size and surface properties.[125] These materials influence the behavior of CAFs either through direct physical interactions or by releasing specific chemical signals, thereby

promoting or inhibiting their pro-tumorigenic functions. For instance, some nanomaterials alter the ETM composition, impacting the support CAFs offer to tumor cell.[16] Nanomaterials in the tumor microenvironment not only serve as carriers for drugs and bioactive molecules,[126] but also enhance treatment efficacy while minimizing effects on healthy tissues.[120] For instance, specific nanomaterials regulate the availability of oxygen and nutrients, promoting tumor cell apoptosis and reducing tumor volume.[107,127,128] Additionally, these nanomaterials can modulate the immune system, targeting and activating various immune cells to bolster the immune response, consequently enhancing the effectiveness of cancer therapies.[93,99] Additionally, nanomaterials show therapeutic potential by regulating CAF roles in immune responses, angiogenesis, and tumor tissue stiffening.[96,129] For example, certain nanomaterials influence the physical and chemical dynamics of the tumor microenvironment. They disrupt angiogenesis in tumors and regulate the secretion of growth factors by tumor-associated fibroblasts, effectively inhibiting tumor growth and metastasis.[101,103] Despite challenges such as targeting precision and potential off-target effects, current research emphasizes improving nanomaterial design to overcome these issues.[130] Overall, nanomaterial and CAFs interactions deepen our understanding of the TME's complexity and pave the way for innovative anticancer strategies. However, further research and clinical trials are essential to optimize the use of nanomaterials and ensure their safety in clinical applications.

## Nanoscale Drug Delivery Systems Targeting CAFs for Cancer Treatment

Although nanomedicine delivery systems have more advantages than traditional drug therapy.[131–133] Nanomedicine faces numerous challenges in entering tumors,[134] especially its therapeutic effects in solid tumors and proliferative connective tissue tumors are limited.[135] Therefore, it is necessary to take measures to enhance the penetration and permeability of nanomedicines to strengthen drug delivery capability.[136–138] In this regard, we have introduced some enhanced delivery system approaches (Figure 4).

### Gene-Related Drug Delivery Systems Targeting CAFs

Traditionally, studying DNA and RNA is fundamental approach in biology. In one study, researchers invented a polymer called Polymeric Vinyl Resin (PVR) and combined it with plasmids encoding Relaxin (RLN) to form lipid nanoparticle complexes (LPPR), aiming to enhance gene transfer efficiency and reduce toxicity, this approach resulted in inhibiting CAF proliferation and tumor growth.[139] 5-Fluorouracil (5-FU) is a DNA synthesis inhibitor, blocks the normal thymine nucleotide biosynthesis pathway, preventing tumor cells and CAFs from growing and dividing normally, although it also affects normal cells. However, Handali et al in the study found that a new folate liposome can more effectively deliver fluorouracil to cancer cells and reduce toxicity.[140] Similarly, in another new study, Jain et al discovered that certain microRNAs can enhance the sensitivity of colorectal cancer radiotherapy by regulating tumor cell apoptosis, DNA damage repair pathways.[115] Meanwhile, in a study by Sheng et al, a CAF-targeted poly (lactic-co-glycolic acid) (PLGA) nanoemulsion was used to simultaneously deliver doxorubicin (DOX) and small interfering RNA (siRNA) targeting hepatocyte growth factor (HGF) for chemotherapy and gene therapy. The results were surprising to find that the delivered siRNA reduced the expression of HGF in the remaining CAFs, thus overcoming the chemotherapy-induced upregulation of HGF mRNA and preventing the increment of CAFs through an autocrine HGF closed loop.[82] Due to these synergistic effects, tumor proliferation, migration, and invasion were significantly inhibited, and tumor permeability was significantly improved. Furthermore, it is well known that siRNA is a type of small RNA, and inhibits gene expression by interfering with the stability and translation of targeted mRNA molecules. At present, many studies have proved that siRNA can be encapsulated into cells by liposomes to inhibit the gene expression of tumor cells,[141,142] but there are only a few studies that have shown that siRNA may also act on CAFs to inhibit the biological function expression of CAFs,[143,144] so we look forward to more research in this field in the future. Lastly, in a special study, researchers discovered a dual-labeled nanoprobe based on small extracellular vesicles (sEVs) that can be utilized for tumor detection and diagnosis.[145] This nanoprobe can also serve as a potent tool for studying the biological behaviors of nanosystems in drug delivery, showing significant potential for future applications.

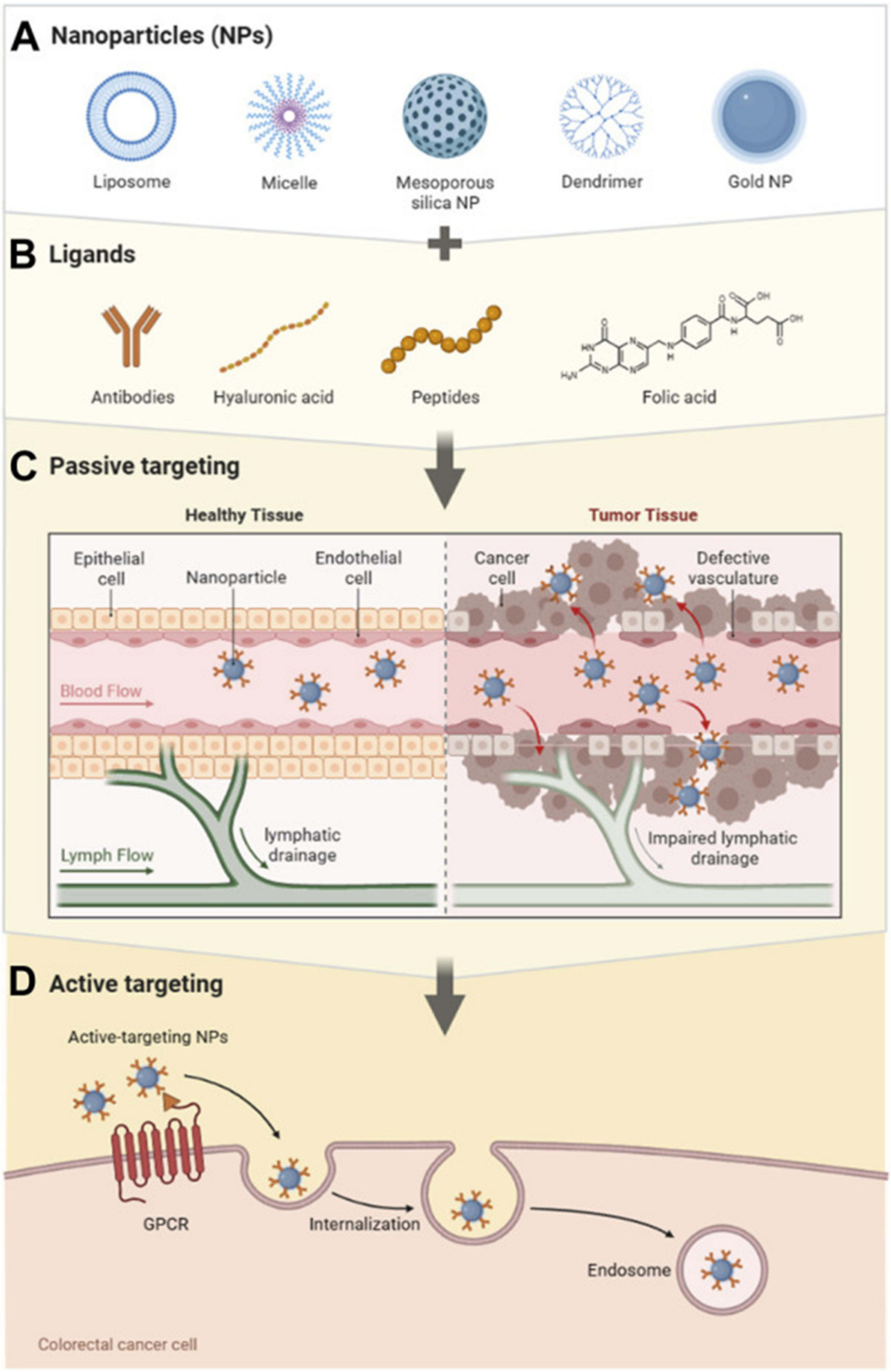


**Figure 4** Mechanisms of Tumor Targeting Mediated by Nanomedicine. (**A**) Various types of nanoparticles (NPs), including liposomes, micelles, mesoporous silica NPs, dendrimers, and gold NPs, serve as versatile carriers for drug delivery. (**B**) Functionalization with ligands such as antibodies, hyaluronic acid, peptides, and folic acid enhances their specificity for CAFs and other TME components. (**C** and **D**) Tumor targeting by nanomedicine is mediated through both passive and active mechanisms. Passive targeting exploits the enhanced permeability and retention effect, allowing nanoparticles to accumulate in tumor tissues with leaky vasculature and impaired lymphatic drainage. Active targeting, on the other hand, uses ligand-functionalized nanoparticles to specifically bind to receptors, such as GPCR, on tumor cells or CAFs, facilitating receptor-mediated internalization and endosomal delivery. These mechanisms enhance precision in drug delivery and improve therapeutic efficacy in modulating the TME. Reproduced from Chang Y, Ou Q, Zhou X, et al. Mapping the intellectual structure and landscape of nano-drug delivery systems in colorectal cancer. Front Pharmacol. 2023;14:1258937. https://creativecommons.org/licenses/by/4.0/.[134].


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## Small Molecule Loaded Drug Delivery System

At present, many small molecule drugs have been used to treat cancer and improve the TME,[16] indicating that small molecule drugs have many advantages in targeting CAFs and cancer immunotherapy. Here, we summarize the latest small molecule-loaded drugs for targeted treatment of CAFs. Nano drug carriers, such as Cellax-DTX nanoparticles, can deliver chemotherapy drugs with high specificity to CAFs, promoting CAF apoptosis and modulating TME. Moreover, Leopoldo Sitia et al used functionalized H-ferritin nanocages and combined them with fragments of FAP antibodies to prepare highly affinity drug carriers.[146] Duan designed a dual-targeted liposome-hybrid micelle system (RPM@NLQ) triggered by matrix metalloproteinase (MMP), sequentially delivering quercetin (Que) and paclitaxel (PTX) to target CAFs, thereby downregulating Wnt16 expression in CAFs to enhance fibrosis improvement.[147] Furthermore, a special nanoemulsion (NE) system can deliver anti-fibrotic drug fraxinellone (Frax) to CAFs, meanwhile researchers also noted that Frax NE combined with tumor-specific peptide vaccines may be an effective and safe strategy.[145] Other small molecule compounds like superparamagnetic iron oxide nanoparticles (SPIONs) could target fibroblast growth factor 2 (FGF2) precursors in CAFs to inhibit their production, while also enhancing the efficacy of gemcitabine.[148] Admittedly, Clara et al's study demonstrated that hydrogen peroxide plays a crucial role in the interaction between gold-iron alloy nanoparticles and CAFs.[149] Interestingly, some macromolecules have also been found effective. For example, the nano-composite hydrogel invented by Liu et al[150] and the peptide-Doxorubicin (GFLG-DOX) conjugate of polyamidoamine (PAMAM) dendritic macromolecules invented by Rashed M et al,[151] both can enhance the penetration and efficacy of chemotherapy drugs without damaging healthy tissues.[150]

## Other Immunotherapy Strategies Targeting CAFs

Targeting CAFs is an important part of the cancer treatment process. Nowadays, researchers are exploring the use of antibodies or other ligands to specifically bind to receptors on the surface of CAFs, thereby inducing their apoptosis or inhibiting their growth. For example, Liang et al used a peptide-assembled nanosystem to effectively inhibit the metastasis of CAFs and prostate cancer.[152] Additionally, there are methods to reprogram CAFs, for example, CAF metabolic reprogramming to control glucose uptake and lactate production to design specific drug-targeting strategies.[94,153] For instance, Theivendran S et al used DMON-P to reprogram CAFs, downregulate CAF biomarkers, and effectively deliver Dox to inhibit tumor growth.[154] Meanwhile, multiple studies have found that DNA-targeted vaccines have multiple biological advantages,[155] for example, Geng et al invented a vaccine targeting tumor cells and FAPα and tumor cell antigen survivin, which can specifically eliminate CAFs, regulate the tumor microenvironment, and enhance T cell-mediated anticancer effects.[156] Regarding vaccines, in a recent study, Hu et al used CAFs as antigens to create vaccines, which stimulate the body to generate an immune response targeting CAFs, thus attacking tumor cells. Finally, their experiments were successful both in vitro and in vivo, so their result indicate that using CAFs as antigens to make vaccines is a feasible cancer treatment method, worthy of further research and exploration.[144] Moreover, introducing activated T cells into the tumor site has been shown to reduce tumor growth. These T cells specifically recognize and attack CAFs, contributing to the inhibition of tumor progression.[141] Liposomes are also common carriers targeting CAFs. For instance, Li et al conjugated scFv to liposomes to utilize the high-affinity binding capability of anti-tumor specific monoclonal antibodies, allowing liposomes to better penetrate tumor tissues and achieve higher therapeutic efficacy, enhancing colorectal cancer treatment.[157] Moreover, we also find a new type of co-loaded liposome targeting the insulin receptor (IR) can specifically reduce CAF activity to inhibit tumors.[158] In the study of Lee et al, they chose an anti-fibrotic drug, nintedanib, to reduce CAFs activation and proliferation, resulting in blocking the platelet-derived growth factor receptor β (PDGFRβ) signaling pathway and reducing its secretion of IL-6 levels to inhibit CAFs.[159]

# Conclusion and Future Research Directions

Previous research indicates that CAFs not only generate extracellular matrix components that make up tumor stroma but also release growth factors, chemokines, exosomes, and metabolites, influencing all tumor characteristics, including drug treatment response.[160] As our understanding of CAFs evolves with ongoing scientific research, broader avenues for targeted immunotherapy based on their characteristics are emerging. Several studies suggest a correlation between PD-L1 expression levels and the degree of CAF enrichment. Specifically, certain CAFs can suppress T-cell activity by secreting

PD-L1, aiding tumor cells in evading immune system attacks. Therefore, research on the relationship between PD-L1 and CAFs is crucial for understanding the regulatory mechanisms of the tumor immune microenvironment and developing more effective tumor therapies.[161–163] In addition to their role in immune suppression, CAFs can also directly influence tumor cell behavior and characteristics by secreting growth factors, activating protein receptor signaling pathways, and regulating gene expression. Therefore, targeting these pathways is crucial for treating cancer. As shown in Table 2 below, we have summarized some current drugs and treatments that aim to inhibit CAFs.

Although in the past few decades, an increasing number of new drugs and treatments have emerged for targeted therapy of CAFs, and the advantages of using nanoplatforms for targeted cancer treatment of CAFs have been magnified, there remains a significant challenge in translating novel nanoplatforms into clinically usable applications. So far, we have observed that the use of responsive biomaterials in the design and preparation of nanomedicines can achieve targeted effects on the tumor microenvironment and CAFs. The growing potential of this approach in clinical applications indicates that it may become a new trend in the future.[174] In fact, in addition to the previously mentioned targeted therapies, new treatment methods are emerging, such as using engineered exosomes with powerful intercellular communication, payload delivery, penetration, and targeting capabilities, making them potent tools for developing next-generation personalized nanomedicines for treatment and diagnosis.[175] Targeting

**Table 2** Drugs for Targeting CAFs in Preclinical and Clinical Trials

| Target | Function | Drug | Mechanism | Preclinical or Clinical Trials | Reference |
|---|---|---|---|---|---|
| PD-L1 | Promote T cell mediated | Adebrelimab (A humanized monoclonal antibody with high affinity) | PD-L1 antibody | Phase II | [161] |
| PD-L1 AND VEGFR | Inhibition of tumor escape and angiogenesis | Avelumab and axitinib | PD-L1 antibody AND tyrosine kinase inhibitor (TKI) | Phase III | [162] |
| TGF-β | Inhibit CAFs activation | Galunisertib | Active inhibitor | Phase II | [164] |
| TGFb | Inhibition of autologous lipase activity | Autogenous lipase inhibitor IOA-289 | Active inhibitor | Preclinical | [165] |
| IGF-1 | Blocking the signal transduction between IGF-1 and its receptor | An inhibitor | Active inhibitor | Preclinical | [166] |
| FGFR2 | Attenuate tumor activity | Futibatinib | FGFR1-4 inhibitor | Phase I | [167] |
| Pin1 | Antibody binding to CAF | DNA encoding microcapsule system (DMS) | Pin1 inhibitor/ Active inhibitor | Preclinical | [168] |
| ZBP1 (Zinc finger binding protein 1) | Inhibition of tumor growth and metastasis by inhibiting mTOR signaling pathway | CBL0137 | A small molecule compound/Activator | Preclinical | [169] |
| Hypoxia inducible factor 1, 2 (HIF1, 2) | Specifically cleave DNA sequences | CRISPR-Cas9 | Dual enzyme system | Preclinical | [170] |
| HIF2 | Inhibit hif2, inhibit cancer cells | Belzutifan | A small molecule compound/ Active inhibitor | Phase III | [170] |
| Wnt2 molecule | Enhance the efficacy of ICI | Anti Wnt2 monoclonal antibody | Anti Wnt2 monoclonal antibody | Preclinical | [171] |
| Integrin αvβ3 | Inducing apoptosis of triple negative breast cancer cells | ProAgio | Protein | Preclinical | [172] |
| Galectin-1 (Gal-1) | Down regulated the production of plasminogen activator inhibitor 2 (PAI-2) | Therapeutic inhibitors (LLS30) | Active inhibitor | Preclinical | [173] |
| CAFs and T cells | Reduce the proliferation and migration of fibroblasts and reduce inflammation | Calcipotriol | Vitamin D analogs | Phase II | [163] |


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tumor-associated macrophages and other cells is also an emerging direction for cancer treatment.[176] Future research should focus on several areas. Firstly, developing more precise and selective nanomedicine delivery systems.[177–179] Specifically, if these drug delivery systems can respond to specific stimuli in the tumor microenvironment such as pH, enzymes, or temperature, improving the targeting accuracy and release kinetics of therapeutic agents.[180–182] In addition, these specificities can minimize systemic toxicity and maximize therapeutic effects on cancer cells and CAFs.[183] Secondly, exploring the synergistic effects of combining CAF-targeted nanomedicines with other treatment modalities, such as immunotherapy, chemotherapy, gene therapy, and photodynamic therapy, can lead to more effective cancer treatments.[179,184–187] For instance, we can integrate gene editing technology and metabolic reprogramming strategies into nanomedicine platforms,[188,189] which can directly modify the genetic and metabolic characteristics of CAFs, thereby disrupting their tumor promoting function and enhancing the efficacy of other therapies. For patients, using combination therapy can help overcome drug resistance, enhance immune system activation, and launch multi-faceted attacks on tumor cells, improving their clinical treatment outcomes.[94] The third is to strengthen the connection between basic research and clinical trials, accelerate the development and clinical use of new targeted drugs.[190,191] Finally, from the perspective of nanomaterials, multifunctional nanomaterials can improve the accuracy of drug delivery by simultaneously targeting multiple aspects of the tumor microenvironment, thereby reducing side effects and improving overall therapeutic outcomes.[93,133] Such nanomaterials could simultaneously target CAFs, deliver therapeutic agents, and regulate immune responses. We hope to see their development and clinical application in the near future. Moreover, we recently discovered that some studies have explored the application of traditional Chinese medicine ingredients in targeted delivery, which represents another effective treatment method.[192,193] So, if nanocarriers can be effectively used to deliver traditional Chinese medicine components with inherent therapeutic properties to CAFs,[194,195] this may provide the possibility of providing novel therapeutic approaches with synergistic effects. However, due to limited current research, there is not sufficient data to extensively discuss this system. We look forward to more research in the future to demonstrate the advantages of using traditional Chinese medicine delivery systems to target CAFs for cancer immunotherapy.

## Abbreviations

CAFs, Cancer-associated Fibroblasts; TME, Tumor Microenvironment; CRC, Colorectal Cancer; ECM, Extracellular Matrix; myCAFs, myofibroblasts; iCAFs, inflammatory CAFs; apCAFs, antigen-presenting CAFs; MSCs, marrow-derived mesenchymal stem cells; TGFβ, Transforming Growth Factor Beta; IL-6, Interleukin-6; α-SMA, α-Smooth muscle actin; FAP, Fibroblast Activation Protein; PDGFR, Platelet-Derived Growth Factor Receptor; FN, fibronectin; LN, laminin; MMPs, matrix metalloproteinases; EPCAM, epithelial cell adhesion molecule; SGR, synovial glycoprotein; MBL, Mannose-binding lectin; OPN, osteopontin; HGF, hepatocyte growth factor; PADC, pancreatic ductal adenocarcinoma; TNF-α, Tumor Necrosis Factor-alpha; MDSCs, myeloid-derived suppressor cells; PD-L1, programmed death ligand 1; AuNPs, Gold nanoparticles; TRF, Transferrin Receptor; MMP-2, Matrix Metalloproteinase-2; PVR, Polymeric Vinyl Resin; RLN, Relaxin; LPPR, lipid nanoparticle complexes; 5-FU, 5-Fluorouracil; PLGA, poly (lactic co-glycolic acid); DOX, deliver doxorubicin; sEVs, small extracellular vesicles; MMP, matrix metalloproteinase; Que, quercetin; FGF 2, fibroblast growth factor 2; NE, nanoemulsion; SPIONs, superparamagnetic iron oxide nanoparticles; PAMAM, polyamidoamine; IR, insulin receptor; TKI, tyrosine kinase inhibitor; VEGFR, Vascular Endothelial Growth Factor Receptor; PAI-2, plasminogen activator inhibitor 2; HIF 1, Hypoxia inducible factor 1; ICI, immune checkpoint inhibitor; ZBP1, Zinc finger binding protein 1; ROS, reactive oxygen species.

## Data Sharing Statement

The data in the manuscript is available. All data can be obtained by contacting the corresponding author.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that there are no competing interests associated with this work.

## References

1. Zhang F, Ma Y, Li D, et al. Cancer associated fibroblasts and metabolic reprogramming: unraveling the intricate crosstalk in tumor evolution. *J Hematol Oncol*. 2024;17(1):80. doi:10.1186/s13045-024-01600-2
2. Zhang C, Fei Y, Wang H, et al. CAFs orchestrates tumor immune microenvironment-A new target in cancer therapy? *Front Pharmacol*. 2023;14:1113378. doi:10.3389/fphar.2023.1113378
3. Mhaidly R, Mechta-Grigoriou F. Fibroblast heterogeneity in tumor micro-environment: role in immunosuppression and new therapies. *Semin Immunol*. 2020;48:101417. doi:10.1016/j.smim.2020.101417
4. Timperi E, Croizer H, Khantakova D, et al. At the interface of tumor-associated macrophages and fibroblasts: immune-suppressive networks and emerging exploitable targets. *Clin Cancer Res off J Am Assoc Cancer Res*. 2024;30(23):5242–5251. doi:10.1158/1078-0432.CCR-24-1690
5. Peng H, Yang M, Feng K, Lv Q, Zhang Y. Semaphorin 3C (Sema3C) reshapes stromal microenvironment to promote hepatocellular carcinoma progression. *Signal Transduct Target Ther*. 2024;9(1):169. doi:10.1038/s41392-024-01887-0
6. Xiang X, Niu YR, Wang ZH, Ye LL, Peng WB, Zhou Q. Cancer-associated fibroblasts: vital suppressors of the immune response in the tumor microenvironment. *Cytokine Growth Factor Rev*. 2022;67:35–48. doi:10.1016/j.cytogfr.2022.07.006
7. Hu JL, Wang W, Lan XL, et al. CAFs secreted exosomes promote metastasis and chemotherapy resistance by enhancing cell stemness and epithelial-mesenchymal transition in colorectal cancer. *Mol Cancer*. 2019;18(1):91. doi:10.1186/s12943-019-1019-x
8. Chen Y, McAndrews KM, Kalluri R. Clinical and therapeutic relevance of cancer-associated fibroblasts. *Nat Rev Clin Oncol*. 2021;18(12):792–804. doi:10.1038/s41571-021-00546-5
9. Liu Y, Ye Z, Yang W, et al. A triple enhanced permeable gold nanoraspberry designed for positive feedback interventional therapy. *J Control Release off J Control Release Soc*. 2022;345:120–137. doi:10.1016/j.jconrel.2022.03.010
10. Hu M, Cheng N, Wang S, et al. Salvianolic acid B-loaded polydopamine-modified hollow mesoporous organic silica nanoparticles for treatment of breast cancer metastasis via suppressing cancer-associated fibroblasts. *Eur J Pharm Sci off J Eur Fed Pharm Sci*. 2024;192:106641. doi:10.1016/j.ejps.2023.106641
11. Kimiz-Gebologlu I, Oncel SS. Exosomes: large-scale production, isolation, drug loading efficiency, and biodistribution and uptake. *J Control Release off J Control Release Soc*. 2022;347:533–543. doi:10.1016/j.jconrel.2022.05.027
12. Cheng Y, Zou J, He M, et al. Spatiotemporally controlled Pseudomonas exotoxin transgene system combined with multifunctional nanoparticles for breast cancer antimetastatic therapy. *J Control Release off J Control Release Soc*. 2024;367:167–183. doi:10.1016/j.jconrel.2023.08.011
13. Zhu Z, McGray AJR, Jiang W, Lu B, Kalinski P, Guo ZS. Improving cancer immunotherapy by rationally combining oncolytic virus with modulators targeting key signaling pathways. *Mol Cancer*. 2022;21(1):196. doi:10.1186/s12943-022-01664-z
14. Tong X, Tang R, Xiao M, et al. Targeting cell death pathways for cancer therapy: recent developments in necroptosis, pyroptosis, ferroptosis, and cuproptosis research. *J Hematol Oncol*. 2022;15(1):174. doi:10.1186/s13045-022-01392-3
15. Han B, Song Y, Park J, Doh J. Nanomaterials to improve cancer immunotherapy based on ex vivo engineered T cells and NK cells. *J Control Release off J Control Release Soc*. 2022;343:379–391. doi:10.1016/j.jconrel.2022.01.049
16. Liu M, Song W, Huang L. Drug delivery systems targeting tumor-associated fibroblasts for cancer immunotherapy. *Cancer Lett*. 2019;448:31–39. doi:10.1016/j.canlet.2019.01.032
17. Rimal R, Desai P, Daware R, et al. Cancer-associated fibroblasts: origin, function, imaging, and therapeutic targeting. *Adv Drug Deliv Rev*. 2022;189:114504. doi:10.1016/j.addr.2022.114504
18. Kobayashi H, Gieniec KA, Lannagan TRM, et al. The origin and contribution of cancer-associated fibroblasts in colorectal carcinogenesis. *Gastroenterology*. 2022;162(3):890–906. doi:10.1053/j.gastro.2021.11.037
19. Zhang H, Yue X, Chen Z, et al. Define cancer-associated fibroblasts (CAFs) in the tumor microenvironment: new opportunities in cancer immunotherapy and advances in clinical trials. *Mol Cancer*. 2023;22(1):159. doi:10.1186/s12943-023-01860-5
20. Tang PCT, Chung JYF, Xue VWW, et al. Smad3 promotes cancer-associated fibroblasts generation via macrophage-myofibroblast transition. *Adv Sci Weinh Baden-Wurtt Ger*. 2022;9(1):e2101235. doi:10.1002/advs.202101235
21. Sahai E, Astsaturov I, Cukierman E, et al. A framework for advancing our understanding of cancer-associated fibroblasts. *Nat Rev Cancer*. 2020;20(3):174–186. doi:10.1038/s41568-019-0238-1
22. Jotzu C, Alt E, Welte G, et al. Adipose tissue-derived stem cells differentiate into carcinoma-associated fibroblast-like cells under the influence of tumor-derived factors. *Anal Cell Pathol Amst*. 2010;33(2):61–79. doi:10.3233/ACP-CLO-2010-0535
23. Ferrer-Mayorga G, Gómez-López G, Barbáchano A, et al. Vitamin D receptor expression and associated gene signature in tumour stromal fibroblasts predict clinical outcome in colorectal cancer. *Gut*. 2017;66(8):1449–1462. doi:10.1136/gutjnl-2015-310977
24. Thiery J. Modulation of the antitumor immune response by cancer-associated fibroblasts: mechanisms and targeting strategies to hamper their immunosuppressive functions. *Explor Target Anti-Tumor Ther*. 2022;3(5):598–629. doi:10.37349/etat.2022.00103

25. Huang J, Tsang WY, Li ZH, Guan XY. The origin, differentiation, and functions of cancer-associated fibroblasts in gastrointestinal cancer. *Cell Mol Gastroenterol Hepatol*. 2023;16(4):503–511. doi:10.1016/j.jcmgh.2023.07.001
26. Cortez E, Roswall P, Pietras K. Functional subsets of mesenchymal cell types in the tumor microenvironment. *Semin Cancer Biol*. 2014;25:3–9. doi:10.1016/j.semcancer.2013.12.010
27. Wang T, Ding G, Wang X, et al. Expression of EPB41L2 in cancer-associated fibroblasts: prognostic implications for bladder cancer and response to immunotherapy. *Arch Med Res*. 2024;55(1):102927. doi:10.1016/j.arcmed.2023.102927
28. Maia A, Wiemann S. Cancer-associated fibroblasts: implications for cancer therapy. *Cancers*. 2021;13(14):3526. doi:10.3390/cancers13143526
29. Foster DS, Januszyk M, Delitto D, et al. Multiomic analysis reveals conservation of cancer-associated fibroblast phenotypes across species and tissue of origin. *Cancer Cell*. 2022;40(11):1392–1406.e7. doi:10.1016/j.ccell.2022.09.015
30. Hu H, Piotrowska Z, Hare PJ, et al. Three subtypes of lung cancer fibroblasts define distinct therapeutic paradigms. *Cancer Cell*. 2021;39 (11):1531–1547.e10. doi:10.1016/j.ccell.2021.09.003
31. Yang D, Liu J, Qian H, Zhuang Q. Cancer-associated fibroblasts: from basic science to anticancer therapy. *Exp Mol Med*. 2023;55 (7):1322–1332. doi:10.1038/s12276-023-01013-0
32. Helms EJ, Berry MW, Chaw RC, et al. Mesenchymal lineage heterogeneity underlies nonredundant functions of pancreatic cancer-associated fibroblasts. *Cancer Discov*. 2022;12(2):484–501. doi:10.1158/2159-8290.CD-21-0601
33. Houthuijzen JM, de Bruijn R, van der Burg E, et al. CD26-negative and CD26-positive tissue-resident fibroblasts contribute to functionally distinct CAF subpopulations in breast cancer. *Nat Commun*. 2023;14(1):183. doi:10.1038/s41467-023-35793-w
34. Simon T, Salhia B. Cancer-associated fibroblast subpopulations with diverse and dynamic roles in the tumor microenvironment. *Mol Cancer Res*. 2022;20(2):183–192. doi:10.1158/1541-7786.MCR-21-0282
35. Li L, Zhou S, Lv N, et al. Photosensitizer-encapsulated ferritins mediate photodynamic therapy against cancer-associated fibroblasts and improve tumor accumulation of nanoparticles. *Mol Pharm*. 2018;15(8):3595–3599. doi:10.1021/acs.molpharmaceut.8b00419
36. Zhang J, Lu S, Lu T, et al. Single-cell analysis reveals the COL11A1+ fibroblasts are cancer-specific fibroblasts that promote tumor progression. *Front Pharmacol*. 2023;14:1121586. doi:10.3389/fphar.2023.1121586
37. Tarbit E, Singh I, Peart JN, Rose'Meyer RB. Biomarkers for the identification of cardiac fibroblast and myofibroblast cells. *Heart Fail Rev*. 2019;24(1):1–15. doi:10.1007/s10741-018-9720-1
38. Alpha-smooth muscle actin-positive cancer-associated fibroblasts secreting osteopontin promote growth of luminal breast cancer - PubMed. Available from: https://pubmed.ncbi.nlm.nih.gov/35690734/. Accessed July 31, 2024.
39. The role of α-smooth muscle actin in fibroblast-mediated matrix contraction and remodeling - PubMed. Available from: https://pubmed.ncbi.nlm.nih.gov/27825850/. Accessed July 31, 2024.
40. WRH-2412 alleviates the progression of hepatocellular carcinoma through regulation of TGF-β/β-catenin/α-SMA pathway - PubMed. Available from: https://pubmed.ncbi.nlm.nih.gov/36912230/. Accessed July 31, 2024.
41. The role of fibroblast activation protein in health and malignancy - PubMed. Available from: https://pubmed.ncbi.nlm.nih.gov/32601975/. Accessed July 31, 2024.
42. Isolation of a novel receptor cDNA establishes the existence of two PDGF receptor genes - PubMed. Available from: https://pubmed.ncbi.nlm.nih.gov/2536956/. Accessed July 31, 2024.
43. Lavie D, Ben-Shmuel A, Erez N, Scherz-Shouval R. Cancer-associated fibroblasts in the single-cell era. *Nat Cancer*. 2022;3(7):793–807. doi:10.1038/s43018-022-00411-z
44. Hernández-Jiménez T, Cruz-Nova P, Ancira-Cortez A, et al. Toxicity assessment of [(177)Lu]Lu-iFAP/iPSMA nanoparticles prepared under GMP-compliant radiopharmaceutical processes. *Nanomater Basel Switz*. 2022;12(23). doi:10.3390/nano12234181
45. Nurmik M, Ullmann P, Rodriguez F, Haan S, Letellier E. In search of definitions: cancer-associated fibroblasts and their markers. *Int J Cancer*. 2020;146(4):895–905. doi:10.1002/ijc.32193
46. Mao X, Xu J, Wang W, et al. Crosstalk between cancer-associated fibroblasts and immune cells in the tumor microenvironment: new findings and future perspectives. *Mol Cancer*. 2021;20(1):131. doi:10.1186/s12943-021-01428-1
47. Zhao Z, Li T, Yuan Y, Zhu Y. What is new in cancer-associated fibroblast biomarkers? *Cell Commun Signal*. 2023;21(1):96. doi:10.1186/s12964-023-01125-0
48. Bartoschek M, Oskolkov N, Bocci M, et al. Spatially and functionally distinct subclasses of breast cancer-associated fibroblasts revealed by single cell RNA sequencing. *Nat Commun*. 2018;9(1):5150. doi:10.1038/s41467-018-07582-3
49. Caramelo B, Zagorac S, Corral S, Marqués M, Real FX. Cancer-associated fibroblasts in bladder cancer: origin, biology, and therapeutic opportunities. *Eur Urol Oncol*. 2023;6(4):366–375. doi:10.1016/j.euo.2023.02.011
50. Ping Q, Yan R, Cheng X, et al. Cancer-associated fibroblasts: overview, progress, challenges, and directions. *Cancer Gene Ther*. 2021;28 (9):984–999. doi:10.1038/s41417-021-00318-4
51. Owen JS, Clayton A, Pearson HB. Cancer-associated fibroblast heterogeneity, activation and function: implications for prostate cancer. *Biomolecules*. 2022;13(1):67. doi:10.3390/biom13010067
52. Sharbeen G, McCarroll JA, Akerman A, et al. Cancer-associated fibroblasts in pancreatic ductal adenocarcinoma determine response to SLC7A11 inhibition. *Cancer Res*. 2021;81(13):3461–3479. doi:10.1158/0008-5472.CAN-20-2496
53. Sun L, Ke M, Yin M, et al. Extracellular vesicle-encapsulated microRNA-296-3p from cancer-associated fibroblasts promotes ovarian cancer development through regulation of the PTEN/AKT and SOCS6/STAT3 pathways. *Cancer Sci*. 2024;115(1):155–169. doi:10.1111/cas.16014
54. CAF secreted miR-522 suppresses ferroptosis and promotes acquired chemo-resistance in gastric cancer - PubMed. Available from: https://pubmed.ncbi.nlm.nih.gov/32106859/. Accessed May 28, 2024.
55. Park D, Sahai E, Rullan A. SnapShot: cancer-associated fibroblasts. *Cell*. 2020;181(2):486–486.e1. doi:10.1016/j.cell.2020.03.013
56. Melissari MT, Chalkidi N, Sarris ME, Koliaraki V. Fibroblast reprogramming in gastrointestinal cancer. *Front Cell Dev Biol*. 2020;8:630. doi:10.3389/fcell.2020.00630
57. Toledo B, Picon-Ruiz M, Marchal JA, Perán M. Dual role of fibroblasts educated by tumour in cancer behavior and therapeutic perspectives. *Int J Mol Sci*. 2022;23(24):15576. doi:10.3390/ijms232415576
58. Schütz S, Solé-Boldo L, Lucena-Porcel C, et al. Functionally distinct cancer-associated fibroblast subpopulations establish a tumor promoting environment in squamous cell carcinoma. *Nat Commun*. 2023;14(1):5413. doi:10.1038/s41467-023-41141-9

59. Zeng F, Gao M, Liao S, Zhou Z, Luo G, Zhou Y. Role and mechanism of CD90+ fibroblasts in inflammatory diseases and malignant tumors. *Mol Med*. 2023;29(1):20. doi:10.1186/s10020-023-00616-7
60. Luo H, Xia X, Huang LB, et al. Pan-cancer single-cell analysis reveals the heterogeneity and plasticity of cancer-associated fibroblasts in the tumor microenvironment. *Nat Commun*. 2022;13(1):6619. doi:10.1038/s41467-022-34395-2
61. Han C, Liu T, Yin R. Biomarkers for cancer-associated fibroblasts. *Biomark Res*. 2020;8(1):64. doi:10.1186/s40364-020-00245-w
62. Cirri P, Chiarugi P. Cancer-associated-fibroblasts and tumour cells: a diabolic liaison driving cancer progression. *Cancer Metastasis Rev*. 2012;31(1–2):195–208. doi:10.1007/s10555-011-9340-x
63. Piwocka O, Piotrowski I, Suchorska WM, Kulcenty K. Dynamic interactions in the tumor niche: how the cross-talk between CAFs and the tumor microenvironment impacts resistance to therapy. *Front Mol Biosci*. 2024;11:1343523. doi:10.3389/fmolb.2024.1343523
64. Fang Z, Meng Q, Xu J, et al. Signaling pathways in cancer-associated fibroblasts: recent advances and future perspectives. *Cancer Commun*. 2023;43(1):3–41. doi:10.1002/cac2.12392
65. L J, R L, L S, et al. The biology, function, and applications of exosomes in cancer. *Acta Pharm Sin B*. 2021;11(9). doi:10.1016/j.apsb.2021.01.001
66. Hajialiasgary Najafabadi A, Soheilifar MH, Masoudi-Khoram N. Exosomes in skin photoaging: biological functions and therapeutic opportunity. *Cell Commun Signal*. 2024;22:32. doi:10.1186/s12964-023-01451-3
67. Advances in the applications of extracellular vesicle for the treatment of skin photoaging: a comprehensive review - PubMed. Available from: https://pubmed.ncbi.nlm.nih.gov/37954453/. Accessed July 8, 2024.
68. Sun S, Zhang Y, Li Y, Wei L. Crosstalk between colorectal cancer cells and cancer-associated fibroblasts in the tumor microenvironment mediated by exosomal noncoding RNAs. *Front Immunol*. 2023;14:1161628. doi:10.3389/fimmu.2023.1161628
69. Donelan W, Dominguez-Gutierrez PR, Kusmartsev S. Deregulated hyaluronan metabolism in the tumor microenvironment drives cancer inflammation and tumor-associated immune suppression. *Front Immunol*. 2022;13:971278. doi:10.3389/fimmu.2022.971278
70. Liu T, Han C, Wang S, et al. Cancer-associated fibroblasts: an emerging target of anti-cancer immunotherapy. *J Hematol Oncol*. 2019;12(1):86. doi:10.1186/s13045-019-0770-1
71. Fibroblast diversity and plasticity in the tumor microenvironment: roles in immunity and relevant therapies - PubMed. Available from: https://pubmed.ncbi.nlm.nih.gov/37723510/. Accessed May 21, 2024.
72. Huang H, Wang Z, Zhang Y, et al. Mesothelial cell-derived antigen-presenting cancer-associated fibroblasts induce expansion of regulatory T cells in pancreatic cancer. *Cancer Cell*. 2022;40(6):656–673.e7. doi:10.1016/j.ccell.2022.04.011
73. Tsoumakidou M. The advent of immune stimulating CAFs in cancer. *Nat Rev Cancer*. 2023;23(4):258–269. doi:10.1038/s41568-023-00549-7
74. Ying F, Chan MSM, Lee TKW. Cancer-associated fibroblasts in hepatocellular carcinoma and cholangiocarcinoma. *Cell Mol Gastroenterol Hepatol*. 2023;15(4):985–999. doi:10.1016/j.jcmgh.2023.01.006
75. Zeng W, Xiong L, Wu W, et al. CCL18 signaling from tumor-associated macrophages activates fibroblasts to adopt a chemoresistance-inducing phenotype. *Oncogene*. 2023;42(3):224–237. doi:10.1038/s41388-022-02540-2
76. Yavuz BG, Pestana RC, Abugabal YI, et al. Origin and role of hepatic myofibroblasts in hepatocellular carcinoma. *Oncotarget*. 2020;11(13):1186–1201. doi:10.18632/oncotarget.27532
77. Chen C, Guo Q, Liu Y, et al. Single-cell and spatial transcriptomics reveal POSTN+ cancer-associated fibroblasts correlated with immune suppression and tumour progression in non-small cell lung cancer. *Clin Transl Med*. 2023;13(12):e1515. doi:10.1002/ctm2.1515
78. Feng J, Xu M, Wang J, et al. Sequential delivery of nanoformulated α-mangostin and triptolide overcomes permeation obstacles and improves therapeutic effects in pancreatic cancer. *Biomaterials*. 2020;241:119907. doi:10.1016/j.biomaterials.2020.119907
79. Kaps L, Schuppan D. Targeting cancer associated fibroblasts in liver fibrosis and liver cancer using nanocarriers. *Cells*. 2020;9(9):2027. doi:10.3390/cells9092027
80. Guo J, Zeng H, Chen Y. Emerging nano drug delivery systems targeting cancer-associated fibroblasts for improved antitumor effect and tumor drug penetration. *Mol Pharm*. 2020;17(4):1028–1048. doi:10.1021/acs.molpharmaceut.0c00014
81. Tang H, Xu X, Chen Y, et al. Reprogramming the tumor microenvironment through second-near-infrared-window photothermal genome editing of PD-L1 mediated by supramolecular gold nanorods for enhanced cancer immunotherapy. *Adv Mater Deerfield Beach Fla*. 2021;33(12):e2006003. doi:10.1002/adma.202006003
82. Shen W, Yao PA, Li W, et al. Cancer-associated fibroblast-targeted nanodrugs reshape colorectal tumor microenvironments to suppress tumor proliferation, metastasis and improve drug penetration. *J Mater Chem B*. 2023;11(9):1871–1880. doi:10.1039/d2tb02253b
83. Najafi M, Farhood B, Mortezaee K. Extracellular matrix (ECM) stiffness and degradation as cancer drivers. *J Cell Biochem*. 2019;120(3):2782–2790. doi:10.1002/jcb.27681
84. Chen X, Jia F, Huang Y, Jin Q, Ji J. Cancer-associated fibroblast-targeted delivery of captopril to overcome penetration obstacles for enhanced pancreatic cancer therapy. *ACS Appl Bio Mater*. 2022;5(7):3544–3553. doi:10.1021/acsabm.2c00486
85. Ghahremanifard P, Chanda A, Bonni S, Bose P. TGF-β mediated immune evasion in cancer-spotlight on cancer-associated fibroblasts. *Cancers*. 2020;12(12):3650. doi:10.3390/cancers12123650
86. Currlin S, Ruedlinger B, Camacho S, et al. Abstract 4552: 3D-EXplore platform of fresh patient tumoroids with intact TME allows assessment of the efficacy of drugs targeting the tumor stroma on ex vivo tumor immunotherapy. *Cancer Res*. 2023;83(7_Supplement):4552. doi:10.1158/1538-7445.AM2023-4552
87. Santagata S, Ieranò C, Trotta AM, et al. CXCR4 and CXCR7 signaling pathways: a focus on the cross-talk between cancer cells and tumor microenvironment. *Front Oncol*. 2021;11:591386. doi:10.3389/fonc.2021.591386
88. Daniel SK, Seo YD, Pillarisetty VG. The CXCL12-CXCR4/CXCR7 axis as a mechanism of immune resistance in gastrointestinal malignancies. *Semin Cancer Biol*. 2020;65:176–188. doi:10.1016/j.semcancer.2019.12.007
89. Biasci D, Smoragiewicz M, Connell CM, et al. CXCR4 inhibition in human pancreatic and colorectal cancers induces an integrated immune response. *Proc Natl Acad Sci U S A*. 2020;117(46):28960–28970. doi:10.1073/pnas.2013644117
90. Singh S, Lamichhane A, Rafsanjani Nejad P, et al. Therapeutic targeting of stromal-tumor HGF-MET signaling in an organotypic triple-negative breast tumor model. *Mol Cancer Res*. 2022;20(7):1166–1177. doi:10.1158/1541-7786.MCR-21-0317

91. Yi Y, Zeng S, Wang Z, et al. Cancer-associated fibroblasts promote epithelial-mesenchymal transition and EGFR-TKI resistance of non-small cell lung cancers via HGF/IGF-1/ANXA2 signaling. *Biochim Biophys Acta Mol Basis Dis*. 2018;1864(3):793–803. doi:10.1016/j.bbadis.2017.12.021
92. Matsumoto K, Umitsu M, De Silva DM, Roy A, Bottaro DP. Hepatocyte growth factor/MET in cancer progression and biomarker discovery. *Cancer Sci*. 2017;108(3):296–307. doi:10.1111/cas.13156
93. Fei B, Mo Z, Yang J, Wang Z, Li S. Nanodrugs reprogram cancer-associated fibroblasts and normalize tumor vasculatures for sequentially enhancing photodynamic therapy of hepatocellular carcinoma. *Int J Nanomed*. 2023;18:6379–6391. doi:10.2147/IJN.S429884
94. Li Z, Sun C, Qin Z. Metabolic reprogramming of cancer-associated fibroblasts and its effect on cancer cell reprogramming. *Theranostics*. 2021;11(17):8322–8336. doi:10.7150/thno.62378
95. He Y, Wu S, Rietveld M, et al. Application of Doxorubicin-loaded PLGA nanoparticles targeting both tumor cells and cancer-associated fibroblasts on 3D human skin equivalents mimicking melanoma and cutaneous squamous cell carcinoma. *Biomater Adv*. 2024;160:213831. doi:10.1016/j.bioadv.2024.213831
96. Lu Q, Kou D, Lou S, et al. Nanoparticles in tumor microenvironment remodeling and cancer immunotherapy. *J Hematol Oncol*. 2024;17:16. doi:10.1186/s13045-024-01535-8
97. Eleraky NE, Allam A, Hassan SB, Omar MM. Nanomedicine fight against antibacterial resistance: an overview of the recent pharmaceutical innovations. *Pharmaceutics*. 2020;12(2):142. doi:10.3390/pharmaceutics12020142
98. Hossen MN, Rao G, Dey A, Robertson JD, Bhattacharya R, Mukherjee P. Gold nanoparticle transforms activated cancer-associated fibroblasts to quiescence. *ACS Appl Mater Interfaces*. 2019;11(29):26060–26068. doi:10.1021/acsami.9b03313
99. Han X, Xu Y, Geranpayehvaghei M, Anderson GJ, Li Y, Nie G. Emerging nanomedicines for anti-stromal therapy against desmoplastic tumors. *Biomaterials*. 2020;232:119745. doi:10.1016/j.biomaterials.2019.119745
100. Gu X, Gao Y, Wang P, et al. Nano-delivery systems focused on tumor microenvironment regulation and biomimetic strategies for treatment of breast cancer metastasis. *J Control Release off J Control Release Soc*. 2021;333:374–390. doi:10.1016/j.jconrel.2021.03.039
101. Liang Q, Zhou L, Li Y, Liu J, Liu Y. Nano drug delivery system reconstruct tumour vasculature for the tumour vascular normalisation. *J Drug Target*. 2022;30(2):119–130. doi:10.1080/1061186X.2021.1927056
102. Xu T, Liu Z, Huang L, Jing J, Liu X. Modulating the tumor immune microenvironment with nanoparticles: a sword for improving the efficiency of ovarian cancer immunotherapy. *Front Immunol*. 2022;13:1057850. doi:10.3389/fimmu.2022.1057850
103. Zhao G, Rodriguez BL. Molecular targeting of liposomal nanoparticles to tumor microenvironment. *Int J Nanomed*. 2013;8:61–71. doi:10.2147/IJN.S37859
104. Kim MG, Shon Y, Kim J, Oh YK. Selective activation of anticancer chemotherapy by cancer-associated fibroblasts in the tumor microenvironment. *J Natl Cancer Inst*. 2017;109(1). doi:10.1093/jnci/djw186
105. Mauro N, Scialabba C, Pitarresi G, Giammona G. Enhanced adhesion and in situ photothermal ablation of cancer cells in surface-functionalized electrospun microfiber scaffold with graphene oxide. *Int J Pharm*. 2017;526(1–2):167–177. doi:10.1016/j.ijpharm.2017.04.045
106. Zhu Y, Wang A, Zhang S, et al. Paclitaxel-loaded ginsenoside Rg3 liposomes for drug-resistant cancer therapy by dual targeting of the tumor microenvironment and cancer cells. *J Adv Res*. 2023;49:159–173. doi:10.1016/j.jare.2022.09.007
107. Qin H, Ding Y, Mujeeb A, Zhao Y, Nie G. Tumor microenvironment targeting and responsive peptide-based nanoformulations for improved tumor therapy. *Mol Pharmacol*. 2017;92(3):219–231. doi:10.1124/mol.116.108084
108. Chen Y, Hu M, Wang S, et al. Nano-delivery of salvianolic acid B induces the quiescence of tumor-associated fibroblasts via interfering with TGF-β1/Smad signaling to facilitate chemo- and immunotherapy in desmoplastic tumor. *Int J Pharm*. 2022;623:121953. doi:10.1016/j.ijpharm.2022.121953
109. Recent advances in drug delivery systems for targeting cancer stem cells - PubMed. Available from: https://pubmed.ncbi.nlm.nih.gov/33532180/. Accessed June 6, 2024.
110. Fourniols T, Bastien E, Canevat A, Feron O, Préat V. Inhibition of colorectal cancer-associated fibroblasts by lipid nanocapsules loaded with acriflavine or paclitaxel. *Int J Pharm*. 2020;584:119337. doi:10.1016/j.ijpharm.2020.119337
111. Kovács D, Igaz N, Marton A, et al. Core-shell nanoparticles suppress metastasis and modify the tumour-supportive activity of cancer-associated fibroblasts. *J Nanobiotechnology*. 2020;18(1):18. doi:10.1186/s12951-020-0576-x
112. Deng H, Yang Y, Zuo T, et al. Multifunctional ZnO@CuS nanoparticles cluster synergize chemotherapy and photothermal therapy for tumor metastasis. *Nanomedicine*. 2021;34:102399. doi:10.1016/j.nano.2021.102399
113. Jiang M, He K, Qiu T, et al. Tumor-targeted delivery of silibinin and IPI-549 synergistically inhibit breast cancer by remodeling the microenvironment. *Int J Pharm*. 2020;581:119239. doi:10.1016/j.ijpharm.2020.119239
114. Liu Q, Chen F, Hou L, et al. Nanocarrier-mediated chemo-immunotherapy arrested cancer progression and induced tumor dormancy in desmoplastic melanoma. *ACS Nano*. 2018;12(8):7812–7825. doi:10.1021/acsnano.8b01890
115. Jain SM, Nagainallur Ravichandran S, Murali Kumar M, et al. Understanding the molecular mechanism responsible for developing therapeutic radiation-induced radioresistance of rectal cancer and improving the clinical outcomes of radiotherapy - A review. *Cancer Biol Ther*. 2024;25(1):2317999. doi:10.1080/15384047.2024.2317999
116. Cun X, Chen J, Li M, et al. Tumor-associated fibroblast-targeted regulation and deep tumor delivery of chemotherapeutic drugs with a multifunctional size-switchable nanoparticle. *ACS Appl Mater Interfaces*. 2019;11(43):39545–39559. doi:10.1021/acsami.9b13957
117. Edis Z, Wang J, Waqas MK, Ijaz M, Ijaz M. Nanocarriers-mediated drug delivery systems for anticancer agents: an overview and perspectives. *Int J Nanomed*. 2021;16:1313–1330. doi:10.2147/IJN.S289443
118. Hu Y, Ran M, Wang B, Lin Y, Cheng Y, Zheng S. Co-delivery of docetaxel and curcumin via nanomicelles for enhancing anti-ovarian cancer treatment. *Int J Nanomed*. 2020;15:9703–9715. doi:10.2147/IJN.S274083
119. Chen B, Zheng K, Fang S, et al. B7H3 targeting gold nanocage pH-sensitive conjugates for precise and synergistic chemo-photothermal therapy against NSCLC. *J Nanobiotechnology*. 2023;21(1):378. doi:10.1186/s12951-023-02078-9
120. Yu Q, Qiu Y, Li J, et al. Targeting cancer-associated fibroblasts by dual-responsive lipid-albumin nanoparticles to enhance drug perfusion for pancreatic tumor therapy. *J Control Release off J Control Release Soc*. 2020;321:564–575. doi:10.1016/j.jconrel.2020.02.040
121. Aljabali AA, Obeid MA, Bashatwah RM, et al. Nanomaterials and their impact on the immune system. *Int J Mol Sci*. 2023;24(3):2008. doi:10.3390/ijms24032008

122. Zhou S, Zhen Z, Paschall AV, et al. FAP-targeted photodynamic therapy mediated by ferritin nanoparticles elicits an immune response against cancer cells and cancer associated fibroblasts. *Adv Funct Mater*. 2021;31(7):2007017. doi:10.1002/adfm.202007017
123. Zheng D, Wan C, Yang H, et al. Her2-targeted multifunctional nano-theranostic platform mediates tumor microenvironment remodeling and immune activation for breast cancer treatment. *Int J Nanomed*. 2020;15:10007–10028. doi:10.2147/IJN.S271213
124. Zhang Z, Ding C, Sun T, Wang L, Chen C. Tumor therapy strategies based on microenvironment-specific responsive nanomaterials. *Adv Healthc Mater*. 2023;12(20):e2300153. doi:10.1002/adhm.202300153
125. Hu Y, Gao S, Khan AR, et al. Tumor microenvironment-responsive size-switchable drug delivery nanosystems. *Expert Opin Drug Deliv*. 2022;19(3):221–234. doi:10.1080/17425247.2022.2042512
126. Yao H, Xu K, Zhou J, Zhou L, Wei S. A tumor microenvironment destroyer for efficient cancer suppression. *ACS Biomater Sci Eng*. 2020;6 (1):450–462. doi:10.1021/acsbiomaterials.9b01544
127. Yuan CS, Deng ZW, Qin D, Mu YZ, Chen XG, Liu Y. Hypoxia-modulatory nanomaterials to relieve tumor hypoxic microenvironment and enhance immunotherapy: where do we stand? *Acta Biomater*. 2021;125:1–28. doi:10.1016/j.actbio.2021.02.030
128. Acidic and hypoxic tumor microenvironment regulation by CaO2-loaded polydopamine nanoparticles - PubMed. Available from: https://pubmed.ncbi.nlm.nih.gov/36577992/. Accessed July 31, 2024.
129. Li M, Zhang F, Su Y, Zhou J, Wang W. Nanoparticles designed to regulate tumor microenvironment for cancer therapy. *Life Sci*. 2018;201:37–44. doi:10.1016/j.lfs.2018.03.044
130. Kang Y, Li S. Nanomaterials: breaking through the bottleneck of tumor immunotherapy. *Int J Biol Macromol*. 2023;230:123159. doi:10.1016/j.ijbiomac.2023.123159
131. Jia M, Zhang D, Zhang C, Li C. Nanoparticle-based delivery systems modulate the tumor microenvironment in pancreatic cancer for enhanced therapy. *J Nanobiotechnology*. 2021;19(1):384. doi:10.1186/s12951-021-01134-6
132. Wang M, Xue W, Yuan H, Wang Z, Yu L. Nano-drug delivery systems targeting CAFs: a promising treatment for pancreatic cancer. *Int J Nanomed*. 2024;19:2823–2849. doi:10.2147/IJN.S451151
133. Xue X, Qu H, Li Y. Stimuli-responsive crosslinked nanomedicine for cancer treatment. *Explor Beijing China*. 2022;2(6):20210134. doi:10.1002/EXP.20210134
134. Chang Y, Ou Q, Zhou X, et al. Mapping the intellectual structure and landscape of nano-drug delivery systems in colorectal cancer. *Front Pharmacol*. 2023;14:1258937. doi:10.3389/fphar.2023.1258937
135. Yunna C, Mengru H, Fengling W, Lei W, Weidong C. Emerging strategies against tumor-associated fibroblast for improved the penetration of nanoparticle into desmoplastic tumor. *Eur J Pharm Biopharm Off J Arbeitsgemeinschaft Pharm Verfahrenstechnik EV*. 2021;165:75–83. doi:10.1016/j.ejpb.2021.05.007
136. Izci M, Maksoudian C, Gonçalves F, et al. Gold nanoparticle delivery to solid tumors: a multiparametric study on particle size and the tumor microenvironment. *J Nanobiotechnology*. 2022;20(1):518. doi:10.1186/s12951-022-01727-9
137. Fang T, Zhang J, Zuo T, et al. Chemo-photothermal combination cancer therapy with ROS scavenging, extracellular matrix depletion, and tumor immune activation by telmisartan and diselenide-paclitaxel prodrug loaded nanoparticles. *ACS Appl Mater Interfaces*. 2020;12 (28):31292–31308. doi:10.1021/acsami.0c10416
138. Zhao X, Pan J, Li W, Yang W, Qin L, Pan Y. Gold nanoparticles enhance cisplatin delivery and potentiate chemotherapy by decompressing colorectal cancer vessels. *Int J Nanomed*. 2018;13:6207–6221. doi:10.2147/IJN.S176928
139. Zhang H, Chen L, Zhao Y, et al. Relaxin-encapsulated polymeric metformin nanoparticles remodel tumor immune microenvironment by reducing CAFs for efficient triple-negative breast cancer immunotherapy. *Asian J Pharm Sci*. 2023;18(2):100796. doi:10.1016/j.ajps.2023.100796
140. Handali S, Moghimipour E, Kouchak M, et al. New folate receptor targeted nano liposomes for delivery of 5-fluorouracil to cancer cells: strong implication for enhanced potency and safety. *Life Sci*. 2019;227:39–50. doi:10.1016/j.lfs.2019.04.030
141. Pei Y, Chen L, Huang Y, et al. Sequential targeting TGF-β signaling and KRAS mutation increases therapeutic efficacy in pancreatic cancer. *Small Weinh Bergstr Ger*. 2019;15(24):e1900631. doi:10.1002/smll.201900631
142. Sohn EJ. MiRNA 3613-5p and MiRNA 3916 rescued the inhibition of cell migration in CNOT2 depleted MDA-MD-231 cells. *Transl Cancer Res*. 2020;9(8):4542–4549. doi:10.21037/tcr-19-2821
143. Suh J, Kim DH, Lee YH, Jang JH, Surh YJ. Fibroblast growth factor-2, derived from cancer-associated fibroblasts, stimulates growth and progression of human breast cancer cells via FGFR1 signaling. *Mol, Carcinog*. 2020;59(9):1028–1040. doi:10.1002/mc.23233
144. Hu Y, Recouvreux MS, Haro M, et al. INHBA(+) cancer-associated fibroblasts generate an immunosuppressive tumor microenvironment in ovarian cancer. *NPJ Precis Oncol*. 2024;8(1):35. doi:10.1038/s41698-024-00523-y
145. Santos-Coquillat A, Herreros-Pérez D, Samaniego R, et al. Dual-labeled nanoparticles based on small extracellular vesicles for tumor detection. *Biol Direct*. 2022;17(1):31. doi:10.1186/s13062-022-00345-7
146. Sitia L, Bonizzi A, Mazzucchelli S, et al. Selective targeting of cancer-associated fibroblasts by engineered H-Ferritin nanocages loaded with navitoclax. *Cells*. 2021;10(2). doi:10.3390/cells10020328
147. Duan H, Liu C, Hou Y, et al. Sequential delivery of quercetin and paclitaxel for the fibrotic tumor microenvironment remodeling and chemotherapy potentiation via a dual-targeting hybrid micelle-in-liposome system. *ACS Appl Mater Interfaces*. 2022;14(8):10102–10116. doi:10.1021/acsami.1c23166
148. Mardhian DF, Vrynas A, Storm G, Bansal R, Prakash J. FGF2 engineered SPIONs attenuate tumor stroma and potentiate the effect of chemotherapy in 3D heterospheroidal model of pancreatic tumor. *Nanotheranostics*. 2020;4(1):26–39. doi:10.7150/ntno.38092
149. de Faria CMG, Bissoli M, Vago R, Spinelli AE, Amendola V. Cytotoxicity of PEG-coated gold and gold-iron alloy nanoparticles: ROS or ferroptosis? *Nanomater Basel Switz*. 2023;13(23). doi:10.3390/nano13233044
150. Liu C, Chiang B, Lewin Mejia D, Luker KE, Luker GD, Lee A. Mammary fibroblasts remodel fibrillar collagen microstructure in a biomimetic nanocomposite hydrogel. *Acta Biomater*. 2019;83:221–232. doi:10.1016/j.actbio.2018.11.010
151. Almuqbil RM, Heyder RS, Bielski ER, Durymanov M, Reineke JJ, da Rocha SRP. Dendrimer conjugation enhances tumor penetration and efficacy of doxorubicin in extracellular matrix-expressing 3D lung cancer models. *Mol Pharm*. 2020;17(5):1648–1662. doi:10.1021/acs.molpharmaceut.0c00083

152. Lang J, Zhao X, Qi Y, et al. Reshaping prostate tumor microenvironment to suppress metastasis via cancer-associated fibroblast inactivation with peptide-assembly-based nanosystem. *ACS Nano*. 2019;13(11):12357–12371. doi:10.1021/acsnano.9b04857
153. Becker LM, O'Connell JT, Vo AP, et al. Epigenetic reprogramming of cancer-associated fibroblasts deregulates glucose metabolism and facilitates progression of breast cancer. *Cell Rep*. 2020;31(9):107701. doi:10.1016/j.celrep.2020.107701
154. Theivendran S, Xian H, Qu J, et al. A pioglitazone nanoformulation designed for cancer-associated fibroblast reprogramming and cancer treatment. *Nano Lett*. 2024;24(15):4354–4361. doi:10.1021/acs.nanolett.3c04706
155. A DNA vaccine expressing an optimized secreted FAPα induces enhanced anti-tumor activity by altering the tumor microenvironment in a murine model of breast cancer - PubMed. Available from: https://pubmed.ncbi.nlm.nih.gov/31202521/. Accessed May 21, 2024.
156. Geng F, Bao X, Dong L, et al. Doxorubicin pretreatment enhances FAPα/survivin co-targeting DNA vaccine anti-tumor activity primarily through decreasing peripheral MDSCs in the 4T1 murine breast cancer model. *Oncoimmunology*. 2020;9(1):1747350. doi:10.1080/2162402X.2020.1747350
157. Li Z, Liu C, Li C, et al. Irinotecan/scFv co-loaded liposomes coaction on tumor cells and CAFs for enhanced colorectal cancer therapy. *J Nanobiotechnology*. 2021;19(1):421. doi:10.1186/s12951-021-01172-0
158. Sun X, Wu Y, Wang X, et al. Beyond small molecules: antibodies and peptides for fibroblast activation protein targeting radiopharmaceuticals. *Pharmaceutics*. 2024;16(3):345. doi:10.3390/pharmaceutics16030345
159. Synergistic therapeutic combination with a CAF inhibitor enhances CAR-NK-mediated cytotoxicity via reduction of CAF-released IL-6 - PubMed. Available from: https://pubmed.ncbi.nlm.nih.gov/36849201/. Accessed May 29, 2024.
160. Rizzolio S, Giordano S, Corso S. The importance of being CAFs (in cancer resistance to targeted therapies). *J Exp Clin Cancer Res CR*. 2022;41(1):319. doi:10.1186/s13046-022-02524-w
161. Yin J, Yuan J, Li Y, et al. Neoadjuvant adebrelimab in locally advanced resectable esophageal squamous cell carcinoma: a phase 1b trial. *Nat Med*. 2023;29(8):2068–2078. doi:10.1038/s41591-023-02469-3
162. Choueiri TK, Larkin J, Pal S, et al. Efficacy and correlative analyses of avelumab plus axitinib versus sunitinib in sarcomatoid renal cell carcinoma: post hoc analysis of a randomized clinical trial. *ESMO Open*. 2021;6(3):100101. doi:10.1016/j.esmoop.2021.100101
163. Gorchs L, Ahmed S, Mayer C, et al. The vitamin D analogue calcipotriol promotes an anti-tumorigenic phenotype of human pancreatic CAFs but reduces T cell mediated immunity. *Sci Rep*. 2020;10(1):17444. doi:10.1038/s41598-020-74368-3
164. Faivre S, Santoro A, Kelley RK, et al. Novel transforming growth factor beta receptor I kinase inhibitor galunisertib (LY2157299) in advanced hepatocellular carcinoma. *Liver Int off J Int Assoc Study Liver*. 2019;39(8):1468–1477. doi:10.1111/liv.14113
165. Pietrobono S, Sabbadini F, Bertolini M, et al. Autotaxin secretion is a stromal mechanism of adaptive resistance to TGFβ inhibition in pancreatic ductal adenocarcinoma. *Cancer Res*. 2024;84(1):118–132. doi:10.1158/0008-5472.CAN-23-0104
166. Spandau DF, Chen R, Wargo JJ, et al. Randomized controlled trial of fractionated laser resurfacing on aged skin as prophylaxis against actinic neoplasia. *J Clin Invest*. 2021;131(19):e150972. doi:10.1172/JCI150972
167. Goyal L, Meric-Bernstam F, Hollebecque A, et al. Futibatinib for FGFR2-rearranged intrahepatic cholangiocarcinoma. *N Engl J Med*. 2023;388(3):228–239. doi:10.1056/NEJMoa2206834
168. Liu J, Wang Y, Mu C, et al. Pancreatic tumor eradication via selective Pin1 inhibition in cancer-associated fibroblasts and T lymphocytes engagement. *Nat Commun*. 2022;13(1):4308. doi:10.1038/s41467-022-31928-7
169. Zhang T, Yin C, Fedorov A, et al. ADAR1 masks the cancer immunotherapeutic promise of ZBP1-driven necroptosis. *Nature*. 2022;606:7914):-594–602. doi:10.1038/s41586-022-04753-7
170. Stromal HIF2 regulates immune suppression in the pancreatic cancer microenvironment - PubMed. Available from: https://pubmed.ncbi.nlm.nih.gov/35216965/. Accessed May 28, 2024.
171. Huang TX, Tan XY, Huang HS, et al. Targeting cancer-associated fibroblast-secreted WNT2 restores dendritic cell-mediated antitumour immunity. *Gut*. 2022;71(2):333–344. doi:10.1136/gutjnl-2020-322924
172. Sharma M, Turaga RC, Yuan Y, et al. Simultaneously targeting cancer-associated fibroblasts and angiogenic vessel as a treatment for TNBC. *J Exp Med*. 2021;218(4):e20200712. doi:10.1084/jem.20200712
173. Tsai YT, Li CY, Huang YH, et al. Galectin-1 orchestrates an inflammatory tumor-stroma crosstalk in hepatoma by enhancing TNFR1 protein stability and signaling in carcinoma-associated fibroblasts. *Oncogene*. 2022;41(21):3011–3023. doi:10.1038/s41388-022-02309-7
174. Biomaterial-based responsive nanomedicines for targeting solid tumor microenvironments - PubMed. Available from: https://pubmed.ncbi.nlm.nih.gov/38399240/. Accessed June 6, 2024.
175. An exosomal strategy for targeting Cuhpedcakt efosi cancer-associated fibroblasts mediated tumors desmoplastic microenvironments - Search Results - PubMed. Available from: https://pubmed.ncbi.nlm.nih.gov/?term=An+exosomal+strategy+for+targeting+++++++++Cuhpedcakt+efosi+cancer-associated+fibroblasts+mediated+tumors+desmoplastic+microenvironments. Accessed May 22, 2024.
176. Jiang J, Mei J, Yi S, et al. Tumor associated macrophage and microbe: the potential targets of tumor vaccine delivery. *Adv Drug Deliv Rev*. 2022;180:114046. doi:10.1016/j.addr.2021.114046
177. Duan S, Sun F, Qiao P, et al. Detachable dual-targeting nanoparticles for improving the antitumor effect by extracellular matrix depletion. *ACS Biomater Sci Eng*. 2023;9(3):1437–1449. doi:10.1021/acsbiomaterials.2c01179
178. Mirhadi E, Mashreghi M, Faal Maleki M, et al. Redox-sensitive nanoscale drug delivery systems for cancer treatment. *Int J Pharm*. 2020;589:119882. doi:10.1016/j.ijpharm.2020.119882
179. Ding Y, Wang Y, Hu Q. Recent advances in overcoming barriers to cell-based delivery systems for cancer immunotherapy. *Explor Beijing China*. 2022;2(3):20210106. doi:10.1002/EXP.20210106
180. Shu Y, Song R, Zheng A, Huang J, Chen M, Wang J. Thermo/pH dual-stimuli-responsive drug delivery for chemo-/photothermal therapy monitored by cell imaging. *Talanta*. 2018;181:278–285. doi:10.1016/j.talanta.2018.01.018
181. Augustine R, Kim DK, Kalva N, Eom KH, Kim JH, Kim I. Multi-stimuli-responsive nanomicelles fabricated using synthetic polymer polylysine conjugates for tumor microenvironment dependent drug delivery. *J Mater Chem B*. 2020;8(26):5745–5755. doi:10.1039/d0tb00721h
182. Jiang X, Fan X, Xu W, et al. Self-assembled peptide nanoparticles responsive to multiple tumor microenvironment triggers provide highly efficient targeted delivery and release of antitumor drug. *J Control Release off J Control Release Soc*. 2019;316:196–207. doi:10.1016/j.jconrel.2019.10.031
183. Wu F, Qiu F, Wai-Keong SA, Diao Y. The smart dual-stimuli responsive nanoparticles for controlled anti-tumor drug release and cancer therapy. *Anticancer Agents Med Chem*. 2021;21(10):1202–1215. doi:10.2174/1871520620666200924110418

184. Tan YN, Huang JD, Li YP, et al. Near-infrared responsive membrane nanovesicles amplify homologous targeting delivery of anti-PD immunotherapy against metastatic tumors. *Adv Healthc Mater*. 2022;11(6):e2101496. doi:10.1002/adhm.202101496
185. Zhang Z, Wang Z, Xiong Y, et al. A two-pronged strategy to alleviate tumor hypoxia and potentiate photodynamic therapy by mild hyperthermia. *Biomater Sci*. 2022;11(1):108–118. doi:10.1039/d2bm01691e
186. Zheng Z, Duan A, Dai R, et al. A "dual-source, dual-activation" strategy for an NIR-II window theranostic nanosystem enabling optimal photothermal-ion combination therapy. *Small Weinh Bergstr Ger*. 2022;18(27):e2201179. doi:10.1002/smll.202201179
187. Affinito A, Quintavalle C, Chianese RV, et al. MCT4-driven CAF-mediated metabolic reprogramming in breast cancer microenvironment is a vulnerability targetable by miR-425-5p. *Cell Death Discov*. 2024;10(1):140. doi:10.1038/s41420-024-01910-x
188. Guo D, Ji X, Xie H, et al. Targeted reprogramming of Vitamin B3 metabolism as a nanotherapeutic strategy towards chemoresistant cancers. *Adv Mater Deerfield Beach Fla*. 2023;35(36):e2301257. doi:10.1002/adma.202301257
189. Huang S, Zhu W, Zhang F, et al. Silencing of Pyruvate Kinase M2 via a metal-organic framework based theranostic gene nanomedicine for triple-negative breast cancer therapy. *ACS Appl Mater Interfaces*. 2021;13(48):56972–56987. doi:10.1021/acsami.1c18053
190. Dasgupta S, Dayagi DY, Haimovich G, et al. Global analysis of contact-dependent human-to-mouse intercellular mRNA and lncRNA transfer in cell culture. *eLife*. 2023:12. doi:10.7554/eLife.83584
191. Yang Q, Zhou Y, Chen J, Huang N, Wang Z, Cheng Y. Gene therapy for drug-resistant glioblastoma via lipid-polymer hybrid nanoparticles combined with focused ultrasound. *Int J Nanomed*. 2021;16:185–199. doi:10.2147/IJN.S286221
192. Zhang LY, Zhang JG, Yang X, Cai MH, Zhang CW, Hu ZM. Targeting tumor immunosuppressive microenvironment for the prevention of hepatic cancer: applications of traditional Chinese medicines in targeted delivery. *Curr Top Med Chem*. 2020;20(30):2789–2800. doi:10.2174/1568026620666201019111524
193. Zheng F, Luo Y, Liu Y, Gao Y, Chen W, Wei K. Nano-baicalein facilitates chemotherapy in breast cancer by targeting tumor microenvironment. *Int J Pharm*. 2023;635:122778. doi:10.1016/j.ijpharm.2023.122778
194. Ma Z, Fan Y, Wu Y, et al. Traditional Chinese medicine-combination therapies utilizing nanotechnology-based targeted delivery systems: a new strategy for antitumor treatment. *Int J Nanomed*. 2019;14:2029–2053. doi:10.2147/IJN.S197889
195. Kang C, Wang J, Li R, et al. Smart targeted delivery systems for enhancing antitumor therapy of active ingredients in traditional Chinese medicine. *Mol*. 2023;28(16):5955. doi:10.3390/molecules28165955